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ORIGINAL ARTICLES

VARIATIONS IN SERUM LIPID CONCENTRATION AND CLINICAL CORONARY DISEASE

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The executive health program was started at the instigation of the Surgeon General of the United States Air Force in the Spring of 1950. The primary aim was the reduction in incidence of clinical manifestations of coronary artery disease among the General officers and civilian executives of Air Force Headquarters. Because of this primary aim, records were organized and laboratory studies were selected to add as much information as possible to the problem of atherosclerosis. In addition to a thorough history and physical examination, the usual routine blood counts, blood chemical examination and urinalysis, special emphasis was placed on a study of the cardiovascular system. In support of the cardiovascular study, serum was examined for: cholesterol, phospholipids, lipoprotein fractionization by the ultracentrifuge and by a special study of electrophoretic patterns. Later, special studies were begun for the purpose of determining the cause of widely varying serum lipid levels. When the work of Seifter and Baeder[1] was published in 1954, attempts to demonstrate their lipid mobilizer factor in certain individuals was done in addition to the other lipid studies. Whether the "lipid mobilizer" factor is the same or just related to the "stress" factor remains to be seen.

The laboratory studies were done at the time of the annual examination and were repeated when the patients returned for any reason. They were requested to return at the first signs of an acute upper respiratory infection, a casual infection such as an infected tooth, when under unusual emotional tension, or for any other reason.

THE POPULATION. The number of individuals recorded had reached 509 by 1 January 1959. Active, up-to-date records are available on 418 individuals; about 150 of these are stationed out of the Washington area and 69 are in the area and are retired. Every

effort is made to retain contact with this group, since their records increase in value as time passes. They offer the opportunity of studying changes in serum lipids after retirement and they are the most stable group in the population. About 20% of the active military personnel rotate into and out of the Washington area every year. When they leave the area their records are consolidated and the important data retained in a special file until their return. Efforts are made to continue these observations while they are on duty at other stations; for the most part, medical officers have been very co-operative and follow-up on these cases has been quite good.

The population consists of General officers and civilian executives of the

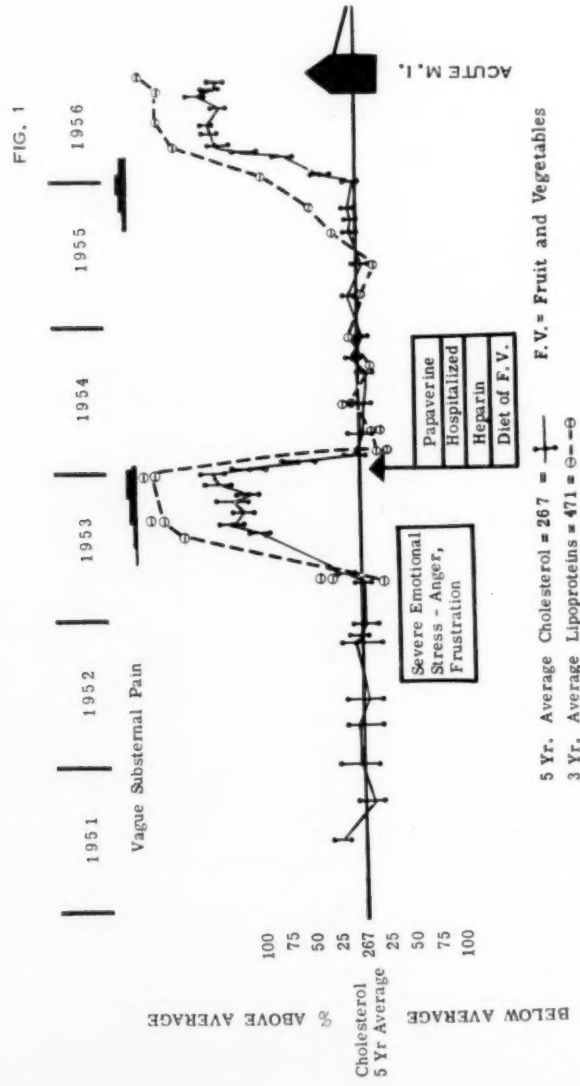
FIG. 1
1951
1952
1953
1954
1955
1956
Vague Substernal Pain
Severe Emotional Stress - Anger, Frustration
Papaverine
Hospitalized
Heparin
Diet of F.V.
ACUTE M.I.
5 Yr. Average Cholesterol = 267 = ┼┼
3 Yr. Average Lipoproteins = 471 = ⊖--⊖
F.V. = Fruit and Vegetables
Graphic chart of one of 16 patients who developed a fatal myocardial infarction. The serum cholesterol determinations were made on aliquots of serum sent to three laboratories simultaneously. Represented by ┼┼ to two laboratories by + one laboratory by -•-. The lipoprotein value is represented by ⊖. The center line represents the five-year average for serum cholesterol and the three-year average for total lipoproteins.
% ABOVE AVERAGE
% BELOW AVERAGE
100
75
50
25
267
25
50
75
100
Cholesterol
5 Yr Average

Fig. 1.—Composite chart of patient showing average cholesterol and lipoprotein with variations in a patient who developed fatal myocardial infarction.

United States Air Force. They are all white males between the ages of 40 and 60 and may be considered to be in excellent health, having been subjected to the eliminating process of yearly physical examinations during their active military life. The factor of greatest importance to this study is their degree of intelligence and wholehearted friendly co-operation with the program. This allows for much closer observations than one usually finds in studying a group of this nature, and as a result, yields much more information concerning emotional stress and other factors.

OBSERVATIONS. One of the first points that was impressed upon us early in the study was the tremendous variations in serum cholesterol, phospholipids and total lipoproteins. Figure 1 demonstrates the variations observed in one patient who eventually developed a myocardial infarction. It is interesting to note that the variation is noted in all 3 laboratories doing cholesterol determinations and in both of the laboratories doing lipoprotein studies. When these flow charts began to illustrate reproducible variations that could be demonstrated in 3 laboratories on 3 aliquots of the same specimen of serum, it was evident that they were not related to laboratory technique.

To determine the relationship between clinical coronary artery disease and serum cholesterol concentration, 177 cases were selected of individuals having had 6 or more cholesterol determinations yearly for at least 5 years. The average for each individual was used to construct the frequency distribution in Fig. 2. While the incidence of coronary disease is weighted on the high end, if one eliminates these 4 cases, the means of the remaining cases will fall within one standard deviation of the mean. In Fig. 3 the same individuals are classified according to percent of variations above the average, using the highest value recorded as the limit of variations. The relationship to clinical heart disease seems to be thoroughly established, in a statistical way at least. This frequency distribution illustrates a point that is not generally discussed among investigators in the field. Namely, there is normally a 25% variation above the average in individuals who have no clinical evidence of heart disease. When evaluating the effects of treatment, one must have multiple observations over a period of several weeks before starting the treatment regimen, then the change in serum cholesterol value must be a consistent one over a period of several weeks or months, corresponding to the treatment period, and this should be reproducible before valid assumptions can be made.

Discussion. The most characteristic factor noticed in the study of the 177 individuals was the variation in serum lipids. Even when 3 laboratories were given aliquots of the same serum, these variations were confirmed. This has been taken as evidence that some unknown factor causes unpredictable variations in the serum lipid concentration. The variations in cholesterol, phospholipids, and in all 3 of the lipoprotein classes were described in relation to emotional stress in 1957 (Groover[2]). This has since been confirmed by Rosenman and Friedman[3]. Dunbar[1], in 1935, concluded that there is a clear-cut personality pattern in many individuals who develop coronary artery disease. Only time will tell what other factors are related to the transient hypercholesterolemia and indeed just how the two are related. The patient described in Fig. 1 of this report died of a fatal myocardial infarction. The lesion found in the circumflex branch of the left coronary artery was not a thrombus. No thrombus was

present. The vessel was occluded by what appeared to be a relatively new atheromatous lesion in which were signs of inflammation, giant cells, new capillaries and swelling of the tissue. no thrombus was found, but a new soft atheromatous lesion in which signs of a foreign body reaction were prominent. One is tempted to develop a hypothesis which would fit the situation

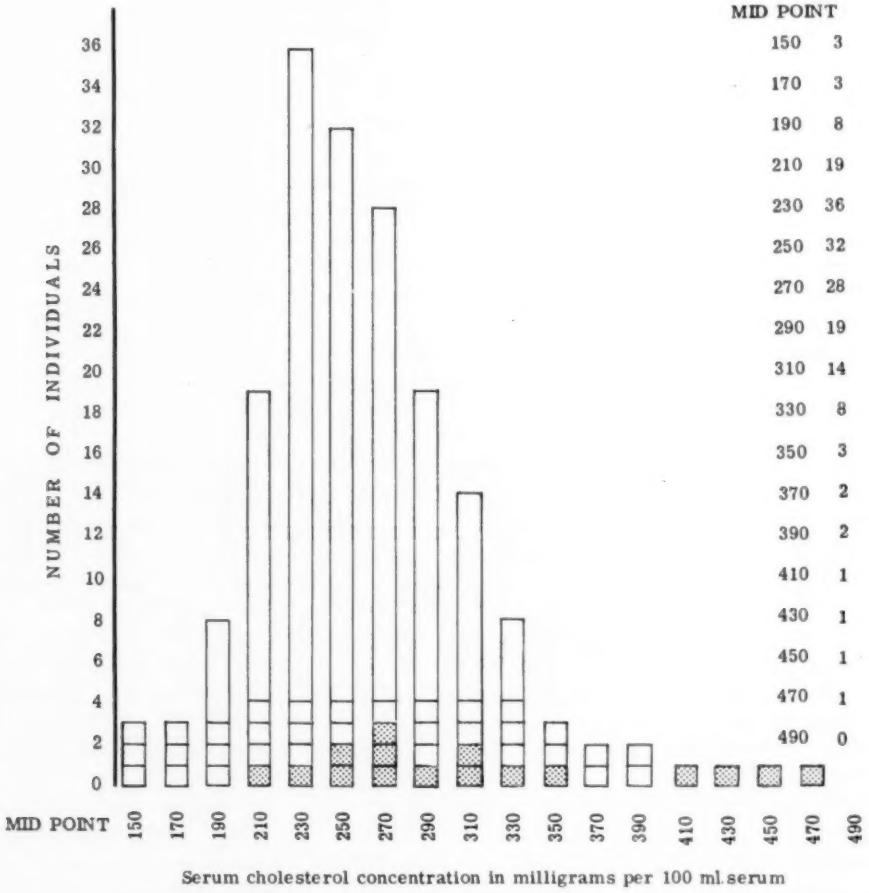

Fig. 2.—Frequency distribution of 181 individuals classified according to the average of all serum cholesterol determinations obtained over a period of 5 years, each individual having 6 or more determinations yearly for the 5-year period. Those having a clinically proven myocardial infarction indicated by the shaded area.

This is taken to be a typical foreign body reaction. In this entire group a total of 31 acute myocardial infarctions have occurred. Six were fatal attacks, death occurring within minutes of the first signs of the attack. In 5 of these

of (1) emotional stress, (2) hypercholesterolemia, (3) post-stress fatigue, which could be interpreted as:

1. Development of atheromatous lesions secondary to transient hypercholesterolemia.

2. Exhaustion of anti-inflammatory hormones of the adrenals during the period of emotional stress.

3. Foreign body reaction with swelling of the atheromatous lesion because of depletion of circulating anti-inflammatory hormones.

The variations in serum cholesterol seem to be more closely related to clinically recognized coronary artery disease, than is the 5-year average. Moreover, in the 16 cases of myocardial infarction noted in Fig. 4 and Fig. 5, a period of abnormal fluctuation preceded each attack. These variations are usually above the 5-year average except in 3 cases in which the fluctuations were diphasic for a period of several weeks before the characteristic upward variations became pronounced (see Fig. 4). Cholesterol seems to be as valuable as any of the other lipid elements for determining the variations in concentration, except for the fact that the variations in total lipoproteins

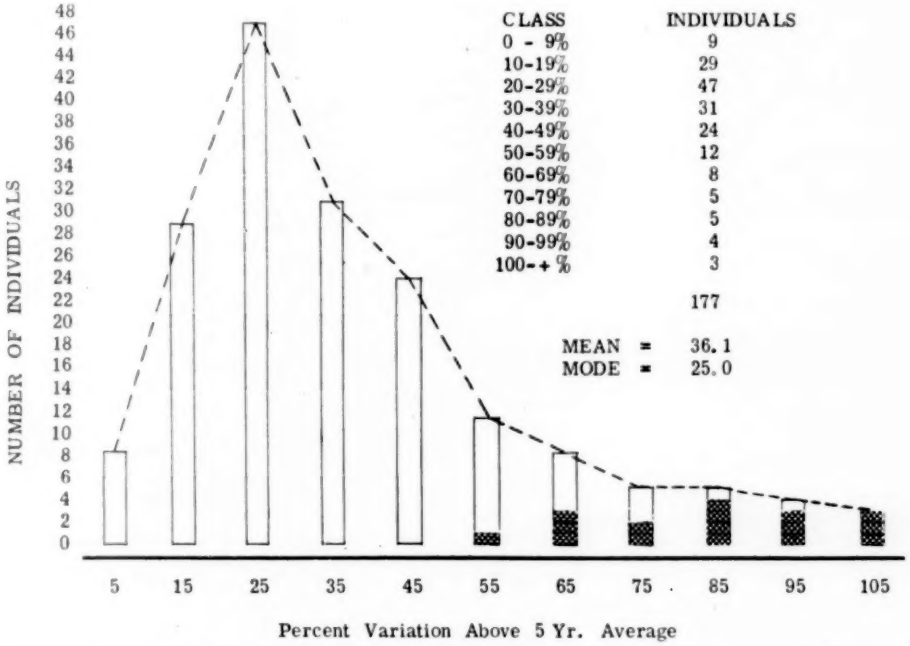

Fig. 3.—Frequency distribution of 177 individuals having had 6 or more serum cholesterol determinations per year for the 5-year period, arranged in classes according to the elevation of the highest serum cholesterol determination recorded for the 5-year period, expressed for each individual as percent above the simple average of all determinations excluding the highest. Those individuals who have developed clinically proven myocardial infarction are indicated by the shaded area.

While this hypothesis is greatly over simplified, the presence of "lipid mobilizer" factor in patients subjected to several types of stress has been demonstrated by our work here, and Zarafonetis, Seifter, Baeder and Kalas[6] have shown the tremendous mobilization of lipids into omental vessels after the stress of surgery. The effects of anti-inflammatory hormone are well known from Selye's[5] works.

occur earlier and are of greater magnitude than are cholesterol values.

Certainly, any one determination is valueless in determining the changes of one individual developing clinical manifestations of coronary disease. A sufficient number of reports must be available to develop a trend.

in most instances. Either the drugs have produced a degree of sedation not compatible with duty, or no effect on serum lipid concentration was noted.

Conclusions. In a group of 177 individuals, 16 cases of clinical myocardial infarction have been observed. The

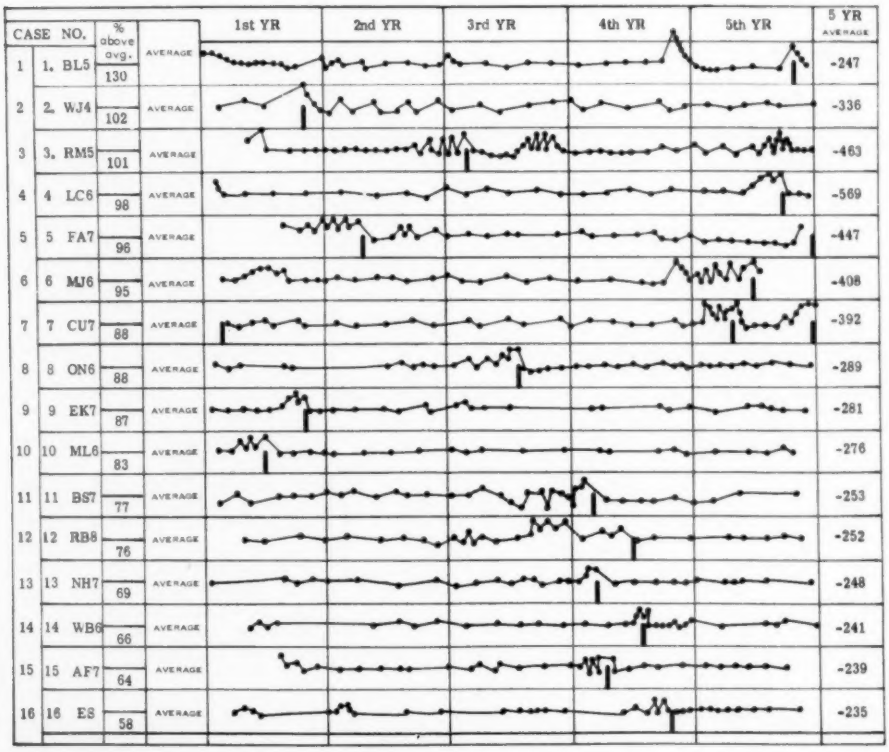
CASE NO.
% above avg.
AVERAGE
1st YR
2nd YR
3rd YR
4th YR
5th YR
5 YR AVERAGE
1 1. BL5 130 AVERAGE -247
2 2. WJ4 102 AVERAGE -336
3 3. RM5 101 AVERAGE -463
4 4 LC6 98 AVERAGE -569
5 5 FA7 96 AVERAGE -447
6 6 MJ6 95 AVERAGE -408
7 7 CU7 88 AVERAGE -392
8 8 ON6 88 AVERAGE -289
9 9 EK7 87 AVERAGE -281
10 10 ML6 83 AVERAGE -276
11 11 BS7 77 AVERAGE -253
12 12 RB8 76 AVERAGE -252
13 13 NH7 69 AVERAGE -248
14 14 WB6 66 AVERAGE -241
15 15 AF7 64 AVERAGE -239
16 16 ES 58 AVERAGE -235

Fig. 4.—Characteristic variations in serum cholesterol from 5-year average for 16 cases of myocardial infarction.

These variations in serum lipid concentration, in our experience, are of such serious consideration that patients are often hospitalized until the picture can be stabilized. Attempts to reduce the serum lipid concentration and stabilize the fluctuating character on a duty status with sedatives and tranquilizers alone have been unsuccessful

cases occurred in the group showing the greatest variations in serum cholesterol. The variations are usually elevated considerably, 25% or more above the 5-year average. The variation of serum lipids seems to be more significant than the concentration in predicting the tendency to develop clinical evidence of coronary disease.

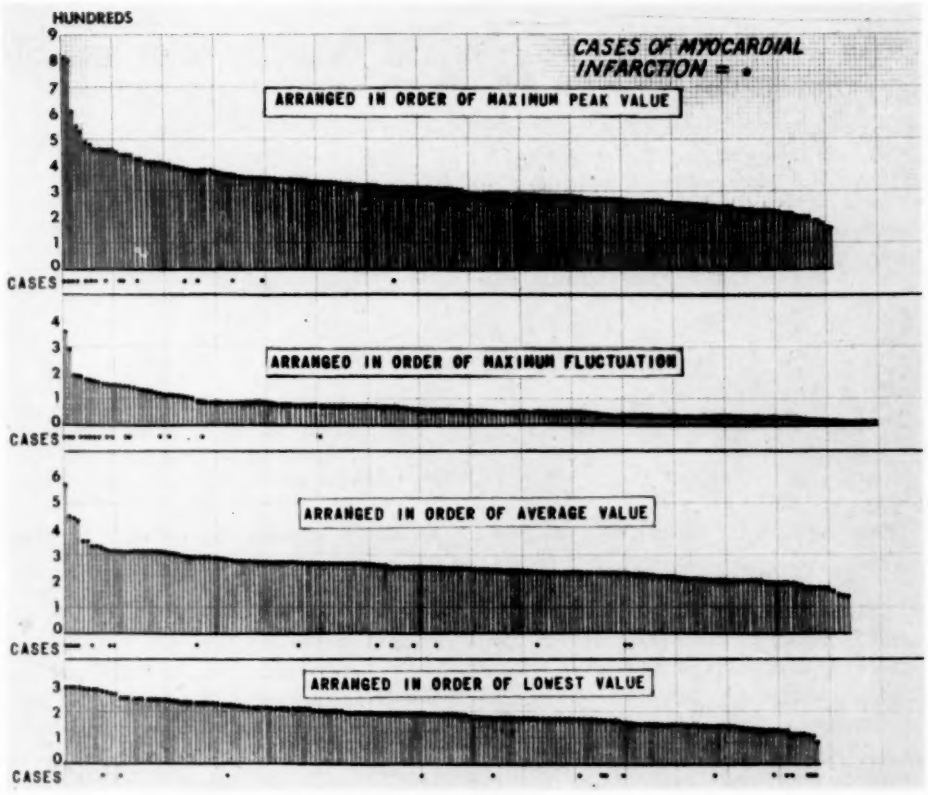

Fig. 5.—Serum cholesterol values of 177 individuals who have had 6 determinations per year for a 5-year period.

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SUMMARIO IN INTERLINGUA

Variationes del Concentration de Lipido in le Sero e Clinic Morbo Coronari

Dece-sex casos de clinic infarcimento myocardial esseva observate in un gruppo de 177 subjectos. Iste casos de infarcimento occurreva in le sub-gruppo exhibiente le plus grande variationes de cholesterol seral. Le variationes esseva usualmente elevate a grados considerabile, attingente 25% o plus supra le quinquenne valores medie. Le variation de lipido in le sero pare esser plus significative que le concentration in predicer le tendentia del disveloppamento de manifestationes clinic de morbo coronari.

RADIOIODINE TRACER TESTS IN THE EVALUATION OF THYROID FUNCTION. RESULTS OF 6-HOUR AND 24-HOUR UPTAKE DETERMINATIONS IN 357 PATIENTS

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Although various reports (Adams and Purves[1], Beck, Kronsbein and Hobbs[2], McConahey, Owen and Keating[3], Storaasli *et al.*[4]) have demonstrated the usefulness of radioiodine (I_{131}) tracer tests in the evaluation of thyroid function, the optimum time for measuring the uptake has been questioned. To distinguish euthyroidism from hyperthyroidism, Storaasli and coworkers[4] found that measurements for radioiodine uptake at 24 hours were reliable in 80 to 90% of their patients. The background count caused by extrathyroidal radioiodine in the neck was considered a disadvantage to an earlier measurement. McConahey, Owen and Keating[3], in appraising 7 parameters of radioiodine testing, found measurements for radioiodine uptake at 6 hours to be the most reliable for evaluating thyroid function in patients with hyperthyroidism and the least reliable in patients with myxedema. In evaluating determinations for radioiodine uptake at 8 and at 48 hours, Adams and Purves[1] found measurements at 8 hours to be more accurate for differentiating euthyroidism from hyperthyroidism. For differentiating hypothyroidism from euthyroidism, the later measurements (at 48 hours) were considered the best index. From their studies, Beck, Kronsbein and Hobbs[2] concluded that the empirically selected time for measurement (24 hours after administration of a dose of radioiodine) was not diagnostically reliable for detecting thyroid dysfunction. They found earlier counts at 4 and at 8 hours to be more dependable and more convenient for the patient. Because these conflicting opinions in the literature concern the most effective time for measuring the radioiodine collected by the thyroid gland, perhaps our experience with the 6-hour and the 24-hour uptake in a series of 357 patients will aid in corroborating the diagnostic usefulness of radioiodine tracer techniques.

Material and Methods. Three hundred and fifty-seven of the 775 patients who had radioiodine tracer studies at this Clinic during a 5-year period from June, 1954, to February, 1959, were chosen for this survey. Four hun-

dred and eighteen patients were excluded because the determinations for radioiodine uptake were made subsequent to surgical treatment, antithyroid drugs, or other medications and diagnostic procedures which could alter the accumulation of radioiodine by the thyroid gland. Diagnoses of euthyroidism, hypothyroidism, or hyperthyroidism were not made on the basis of radioiodine tests alone, but were made after careful correlation of the tracer studies with other clinical and laboratory data.

Each patient while in the fasting state was given a previously counted oral dose of 1 to 2 microcuries of radioiodine in 30 ml. of water. At 6 and at 24 hours following the administration of the radioiodine, readings were made with a collimated scintillation counter fixed at a distance of 15 cm. over the thyroid gland. To compensate for the radioiodine present in the extrathyroidal tissues in the neck, corresponding readings were made over the thigh at a similar 15 cm. distance. The difference between this reading over the thigh and the reading over the thyroid gland was utilized in calculating the percentage of the tracer dose of radioiodine collected by the thyroid glands at the designated intervals.

Results. Of the 357 patients selected for this study, 214 were clinically euthyroid, 41 had hypothyroidism, and 102 revealed hyperthyroidism. For the 214 euthyroid persons, radioiodine uptakes at 6 hours ranged from a low of 7% to a high of 27%, with a mean of 14.33%. The uptakes at 24 hours ranged from 13 to 47%, with a mean of 24.5% (Table 1).

Table 2 shows the results of measurements for radioiodine uptake at 6 and at 24 hours in the patients with hypothyroidism. The range in uptakes at 6 hours was from 1.4 to 9%, with a mean of 4.7%. The 24-hour uptakes ranged from 0.2 to 15%, with a mean of 7%.

Table 3 shows the results of measurements at 6 and at 24 hours in the 102 patients with hyperthyroidism. The range in the uptakes at 6 hours was from 32 to 90%, with a mean of 63.77%. The 24-hour uptakes ranged from 49 to 95%, with a mean of 74.34%.

Discussion. For the euthyroid persons in this series, the 6-hour uptakes were always less than 30% (Fig. 1). In differentiating euthyroidism from hypothyroidism, this early reading was insufficient because the ranges overlapped significantly between 7 and 9%.

TABLE 1.—RADIOIODINE UPTAKE IN 214 EUTHYROID PERSONS

% *Uptake*	*6-Hour Uptake No. Pts.*	*24-Hour Uptake No. Pts.*
6 to 10	24	—
11 to 15	100	3
16 to 20	59	54
21 to 25	25	68
26 to 30	6	42
31 to 35	—	27
36 to 40	—	12
41 to 45	—	5
46 to 50	—	3
Range	7 to 27	13 to 47
Mean	14.33	24.5
S.D. $\bar{x}$	4.3	7.2
S.E. $\bar{x}$	0.2945	0.493

TABLE 2.—RADIOIODINE UPTAKE IN 41 PATIENTS WITH HYPOTHYROIDISM

% *Uptake*	*6-Hour Uptake No. Pts.*	*24-Hour Uptake No. Pts.*
0 to 5	21	19
6 to 10	20	6
11 to 15	—	16
16 to 20	—	—
Range	1.4 to 9	0.2 to 15
Mean	4.7	7.0
S.D. $\bar{x}$	2.33	4.8
S.E. $\bar{x}$	0.364	0.75

TABLE 3.—RADIOIODINE UPTAKE IN 102 PATIENTS WITH HYPERTHYROIDISM

% *Uptake*	*6-Hour Uptake No. Pts.*	*24-Hour Uptake No. Pts.*
31 to 40	8	—
41 to 50	13	1
51 to 60	19	12
61 to 70	18	25
71 to 80	25	24
81 to 90	19	31
91 to 100	0	9
Range	32 to 90	49 to 95
Mean	63.77	74.34
S.D. $\bar{x}$	25.0	10.75
S E. $\bar{x}$	2.49	1.07

Twenty-two of these euthyroid persons (10%) and 12 of the patients with hypothyroidism (29%) had determinations which overlapped.

When the uptakes were determined at 24 hours, 9 of the euthyroid persons (4%) and 8 of the patients with hypothyroidism (19%) had overlapping determinations between 13 and 15%. Although an overlap did occur between the euthyroid and hypothyroid ranges, fewer patients had overlapping determinations than at 6 hours; therefore, the 24-hour uptakes were considered more reliable.

The euthyroid and hyperthyroid ranges did not overlap when the determinations were made at 6 or at 24 hours. At 6 hours, the highest uptake in the euthyroid range was 27%, while the lowest determination in the hyperthyroid range was 32%. From the 24-hour uptakes, the highest determination in the euthyroid range was 47% while the lowest determination in the hyperthyroid range was 49%. The separation between the 2 ranges was wider when the uptake determinations were made at 6 hours than at 24 hours.

Summary. To determine the optimum time for measuring the percentage of a tracer dose of radioiodine collected by the thyroid gland, 357 patients had uptake determinations at 6 and at 24 hours. After careful clinical and laboratory correlation, 214 patients were found to be clinically euthyroid, 41 had hypothyroidism, and 102 revealed hyperthyroidism. When the radioiodine uptake tests were made at 6 hours, the normal and hypothyroid ranges overlapped significantly. The 24-hour uptake showed a smaller percentage of patients with overlapping values; and, therefore, determinations made at this time were considered more reliable for diagnosing hypothyroid disease. The euthyroid and hyperthyroid ranges did not overlap when the uptake determinations were made at 6 hours or at 24 hours, but the separation of the normal and the hyperthyroid ranges was greater when the uptakes were determined at 6 hours.

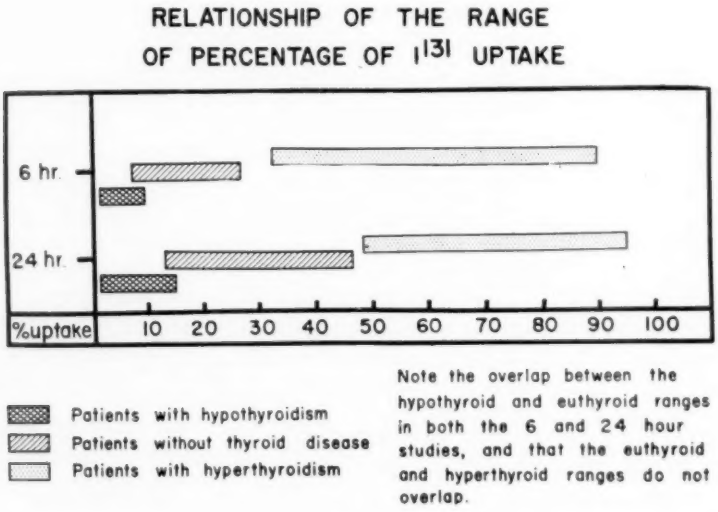
RELATIONSHIP OF THE RANGE
OF PERCENTAGE OF I131 UPTAKE
6 hr.
24 hr.
%uptake
10 20 30 40 50 60 70 80 90 100
Patients with hypothyroidism
Patients without thyroid disease
Patients with hyperthyroidism
Note the overlap between the hypothyroid and euthyroid ranges in both the 6 and 24 hour studies, and that the euthyroid and hyperthyroid ranges do not overlap.

Fig. 1

From this study, we conclude that a determination for radioiodine uptake at 24 hours is more reliable than one at 6 hours for distinguishing hypothyroidism from euthyroidism; whereas, an uptake determination at 6 hours seems sufficient for distinguishing hyperthyroidism from euthyroidism. When feasible, however, radioiodine tracer tests performed at both 6 and 24 hours will serve to evaluate thyroid function better than a single measurement at either interval.

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SUMMARIO IN INTERLINGUA

Tests con Iodo Radioactive Como Traciator in le Evalutation de Function Thyroide. Resultatos de Determinationes del Acceptation post 6 Horas e post 24 Horas in 357 Patientes

Pro determinar qual tempore es le melior pro mesurar le procentage de un dose traciatori de iodo radioactive colligite per le glandula thyroide, determinationes del acceptation post 6 e post 24 horas esseva effectuate in 357 patientes. Super le base de meticulose correlationes clinic e laboratorial, il esseva constatate que 214 del patientes esseva euthyroide, 41 esseva hypothyroide, e 102 esseva hyperthyroide. Quando le tests del acceptation de iodo radioactive esseva facite post un intervallo de 6 horas, le scala del valores in le gruppo normal e le scala del valores in le gruppo hypothyroide monstrava un area significative de coincidentia. Post 24 horas, le coincidentia esseva minus marcate. Per consequente, determinationes effectuate post 24 horas esseva considerate como plus digne de confidentia in le diagnose de morbo hypothyroide. Les scalas del valores de acceptation de iodo radioactive in le gruppo euthyroide e in le gruppo hyperthyroide non coincideva quando le determinationes esseva effectuate post 6 horas, ni quando illos esseva effectuate post 24 horas, sed le separation del scalas pro le gruppo normal e le gruppo hyperthyroide esseva plus grande quando le acceptation esseva determinate post 6 horas.

Super le base de iste studio, nos conclude que le determination del acceptation de iodo radioactive post 24 horas es plus digne de confidentia que un post 6 horas pro distinguer inter hypothyroidismo e euthyroidismo, durante que un determination del acceptation post 6 horas pare sufficer pro distinguer inter euthyroidismo e hyperthyroidismo. Tamen, in tanto que possibile, tests con iodo radioactive como traciator deberea esser effiectuate post 6 e post 24 horas, proque le duo mesurationes servi melio a evalutar le function thyroide que un sol mesuration, sia post 6 o sia post 24 horas.

URINARY OSMOLAR CONCENTRATION: A MEANS OF EVALUATING EARLY RENAL FUNCTION CHANGES IN ESSENTIAL HYPERTENSION*

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It is well known that in the initial stages of essential hypertension, the commonly used renal function studies (blood urea nitrogen, Fishberg concentration, phenolsulfonphthalein, intravenous urogram and creatinine clearance) are normal. Although most of these tests are within normal range varying degrees of renal vascular changes and parenchymal damage may be present (Saltz, Sommers and Smithwick[11]). A means of detecting impairment of renal function in the early stages would be of importance.

It has been shown that in normal patients there is a correlation between the urinary specific gravity and the urinary osmolar concentration (Rappaport *et al.*[10], Frank *et al.*[6]). On the other hand, patients with renal disease do not show this correlation (Rappaport *et al.*[10], Frank *et al.*[5,6], Hooper, Bolomey and Wennesland[7]). As early as 1908, a decrease in urinary concentrating ability was observed in hypertensive patients (Smith[12]). More recently, Frank, Dreifus, Rarick and Bellet[6] noted, in the presence of various types of renal disease, a decreased ability of the kidneys to excrete concentrated urine (800 mOsm. per L. or greater) under hydropenic conditions, although the renal function tests mentioned above were within normal limits. It is the purpose of this study to establish a more exact and accurate evaluation of renal function when the usual tests of renal dynamics appear to be normal.

Material and Methods. A total of 45 observations on 36 patients with a diagnosis of essential hypertension was studied. Patients with chronic pyelonephritis, chronic glomerulonephritis, advanced generalized arteriosclerosis and pheochromocytoma were excluded. In addition, patients were selected only if renal function studies (blood urea nitrogen, Fishberg concentration, urea, creatinine clearance, intravenous urogram and urinalysis) were normal. The cases studied had diastolic pressures of 100 mm. Hg or greater (ranging from 100 mm. Hg to 170 mm. Hg) and a systolic pressure ranging from 150 mm. Hg to 265 mm. Hg. The average mean diastolic pressure was 118 mm. Hg and the average mean systolic pressure was 185 mm. Hg.

The subjects were given a dry supper and all food and water withheld from 6:00 p.m. to 8:00 a.m. the next day. The bladder was then emptied at 8:00 a.m. and a 2-hour urine specimen collected. The specific gravity of the urine was determined by means of an ordinary hydrometer. The urinary osmolar concentration† was determined by the meth-

*This work was aided by a grant from the United States Public Health Service, Grant H 141 (C8).

†Plasma osmotic pressure is relatively stable under fasting conditions and was therefore not routinely performed.

od of depression of the freezing point, using the Fiske osmometer (Corcoran[2]). Blood urea nitrogen was determined according to the method of Folin and Wu[4] and blood and urinary creatinine determined according to the method of Karr[8].

Results. There was no absolute correlation between the urinary specific gravity and the urinary osmolar concentration (Fig. 1). As seen in Fig. 1, the urinary osmolar concentration of 32 of 36 patients was less than 800 mOsm. per L. In the 4 other patients, the urinary osmolar concentration did not exceed 950 mOsm. per L. A breakdown of the 32 patients with urinary osmolar concentrations less than 800 mOsm. per L. showed that in 15 patients the values ranged from 600 to 799 mOsm. per L., and in 17 patients the values were from 400 to 600 mOsm. per L. None of the patients showed urinary osmolar concentrating values below 400 mOsm. per L. No significant correlation was noted between the urea or creatinine clearance and the urinary osmolar concentration. Likewise, there was no correlation of mean blood pressure in mm. Hg with the level of urinary osmolar concentration in mOsm. per L. (Fig. 2).

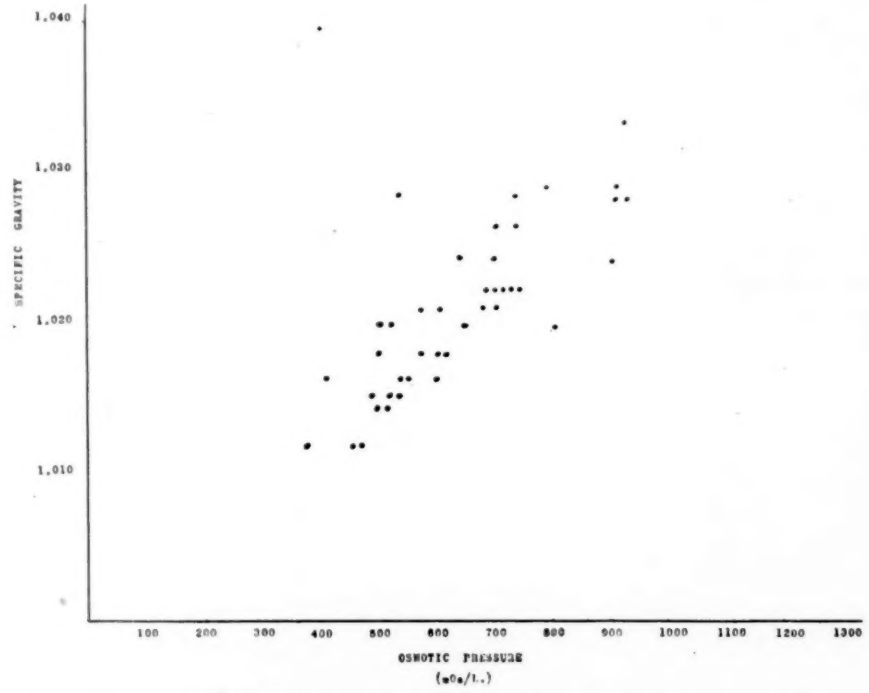

Fig. 1.—There is no absolute correlation between the urinary specific gravity and the osmotic pressure (in mOsm. per L.). Furthermore, despite urinary osmotic concentration values below 500 mOsm. per L., none showed urinary specific gravities below 1.010.

Berliner and associates[1] consider the normal urinary osmolar concentration to vary from 1000 to 1400 mOsm. per L. A previously reported value in normals from this laboratory (Frank *et al.*[6]) showed a mean value of 1076 ± 167 mOsm. per L. (using two standard devi-

ations from the mean, the range for normals varies from 741 to 1410 mOsm. per L.). We then note that 89% of the cases in this present series had urinary osmotic concentration of less than 741 mOsm. per L. and would therefore be considered as having a diminished capacity for concentrating urine.

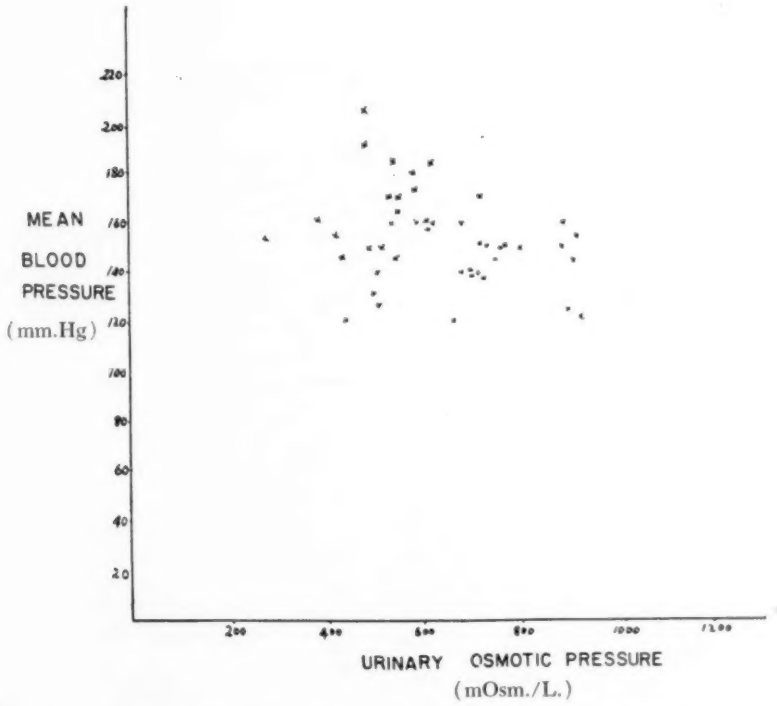

Fig. 2.—The scattergram shows the absence of definite correlation between the level of the mean blood pressure (mm. Hg) and the urinary osmotic pressure (mOsm. per L.).

Discussion. It is recognized that in the early stages of hypertension, even with normal renal function tests, vascular changes are noted microscopically (Saltz, Sommers and Smithwick[11]). It is understandable that measurement of the renal tubular concentrating ability in the hydropenic state by means of the total urine solute concentration would indicate relatively small changes in renal concentrating function. It is quite possible that methods utilizing free water clearance in mannitol-loaded individuals (Raisz, Au and Scheer[9]) would show an even greater derangement in renal tubular function.

From the data presented, it is evident that the concentrating function of the kidney is impaired before urea or creatinine clearance, blood urea nitrogen and Fishberg concentration tests indicate this derangement. Furthermore, the degree of this alteration in the concentrating ability of the kidneys was not related to the diastolic or mean blood pressures. Furthermore, in patients in whom the urinary osmolar concentration fell below 400 mOsm. per L.,

renal impairment was quite severe and in many instances azotemia and renal failure ensued.

Several factors may be involved in bringing about this detectable decrease in tubular concentrating ability in hypertensive patients. Early microscopic vascular and subsequent renal tubular cell changes, and decreased total renal medullary blood flow with resultant decrease in water reabsorption may account for the findings noted (Berliner *et al.*[1], Zak, Brun and Smith[13]).

The finding of a decrease in urinary osmolar concentration in essential hypertension where ordinary tests appear normal, suggests that osmolar concentration would be a valuable test for the early detection of renal tubular disease as well as an index of the prognosis and efficacy of therapy (Dreifus, Lisan and Moyer[3]).

Summary. 1. A total of 45 observations were made on 36 hypertensive patients demonstrating normal renal function with usual renal function tests (blood urea nitrogen, Fishberg concentration, phenolsulfonphthalein, intravenous urogram, and creatinine clearance). The urinary osmolar concentration under hydropenic conditions in 32 of the 36 patients was less than 800 mOsm. per L., indicating impairment in renal concentrating ability.

2. The earliest detectable impairment in renal function in essential hypertension seems to be its capacity to concentrate urine under hydropenic conditions.

3. The determination of urinary osmolar concentration is a simple and rapid test and may serve as a valuable guide in following kidney function prognosis and evaluating the efficacy of the therapeutic regimen instituted in essential hypertension.

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(Interlingua on page 153)

THE USE OF SYROSINGOPINE (SU-3118) AND HYDRALAZINE IN AMBULATORY HYPERTENSIVE PATIENTS

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Rauwolfia serpentina or its constituents form the cornerstone of treatment of diastolic hypertension. These alkaloids have enjoyed widespread popularity because of their effectiveness when given orally in milder hypertensive patients and also because of their unique complementary activity when used in conjunction with more potent antihypertensive agents. These desired pharmacologic activities include: 1) specific blood pressure lowering effect; 2) tranquilization; 3) bradycardia (frequently desired particularly upon the addition of antihypertensive agents tending to produce tachycardia); 4) increased intestinal peristalsis.

It is to be expected that drugs possessing such diverse pharmacologic activity would yield somewhat varying results when the overall effect is compared in individual patients, for example, a desired pharmacologic action in one patient may prove to be an undesired by-effect in a second. The actual incidence of the by-effects is difficult to determine because of their similarity to symptoms produced by hypertension itself and because there sometimes appears to be no direct dosage relationship. In a small series utilizing reserpine, we noted undesirable by-effects in 55% of the patients[3]. In general, these undesirable pharmacologic actions tend to be similar with all the naturally occurring drugs of the Rauwolfia class, including the whole root, even though a difference in the incidence of their side effects has been suggested (Ford and Moyer[4]). The by-effects in question have been enumerated elsewhere (Dunsmore *et al.*[3], Ford and Moyer[4]).

While many patients can be adequately managed with existing medications, the preceding statements indicate a definite need for a drug of the Rauwolfia class possessing equal antihypertensive activity but fewer side effects than the older agents. Syrosingopine*, a synthetic analog of reserpine, was developed to satisfy this need, and its properties in this regard have been demonstrated in several animal species (Plummer *et al.*[6]) as well as in humans (Barbour *et al.*[1], Darvill[2], Herrmann *et al.*[5]). The purpose of our study was to test the antihypertensive action of syrosingopine in humans and to evaluate the complementary action of this new drug and hydralazine† in combined therapy.

Methods and Materials. Syrosingopine was administered to a total of 64 hypertensives in this study. Forty-nine cases were patients attending the Hypertension Clinic of the Philadelphia General Hospital. An additional 15 private patients augmented the series.

*Singoserp brand syrosingopine CIBA.

†Apresoline brand hydralazine (N.N.R.) CIBA.

Medical profiles were obtained consisting of a complete history, physical examination, and the following laboratory studies: hemoglobin, white blood cell count and differential, urinalysis, chest roentgenogram, electrocardiogram, Fishberg concentration test, phenolsulfonphthalein excretion test, Regitine* test for pheochromocytoma, and intravenous pyelography. Each patient exhibited a profile abnormality in at least one area.

Basal diastolic blood pressures were obtained by averaging numerous resting pressures and by an evaluation of previous hospitalization records. All patients were seen at one to 2-week intervals. A 10-minute supine resting blood pressure, a 3-minute standing blood pressure, and finally a sitting blood pressure were obtained upon each patient. The presence or absence and the degree of severity of 26 symptoms were ascertained at each visit.

Those patients on prior therapy were maintained on the same diet, but all antihypertensive agents were discontinued. Syrosingopine therapy was instituted with a dosage of 1 mg. four times daily. If, after a period of 2 to 3 weeks, a satisfactory antihypertensive effect had not been obtained, this dosage was increased to 2 mg. four times daily. If satisfactory blood pressure control was obtained, the dosage was decreased to obtain the actual individual dose required. Hydralazine was added to the regimen in those not satisfactorily controlled with syrosingopine alone, and the dose increased to tolerance, or until a satisfactory blood pressure level was achieved, in the usual manner. Finally, an identical placebo was substituted for the syrosingopine in 20 patients for a period of one month. Patient data are presented in Table 1.

TABLE 1.—PATIENT DATA.

Patients Treated With Syrosingopine

	Syrosingopine	*Syrosingopine and Hydralazine*
Number of Patients	64	39
Male	24	16
Female	40	23
Negro	50	26
Caucasian	14	13
Age: Range	29–78	29–78
Average	47.7	49.4
Smithwick Classification:		
Group I	8	2
II	25	8
III	2	2
IV	29	17
Syrosingopine Daily Dose Range	0.25–12 mg.	1–8 mg.
Hydralazine Daily Dose Range		40–400
Duration of Therapy:		
Range	1–21 months	1–12 months
Average	9 months	7.2 months

Results. The antihypertensive effects of syrosingopine administered alone in 64 patients are summarized in Table 2. A significant diastolic blood pressure response was considered to be the establishment of a diastolic blood pressure of less than 90 mm. of mercury or a supine reduction of at least 20 mm. Slight diastolic reduction was considered to be less than 20 but greater than 10 mm. These results are similar to those which might be anticipated with the use of reserpine, since generally the mildest degree of hypertension responds the most favorably. More than 70% of this group demonstrated a satisfactory blood pressure reduction while only 15% of the severe group achieved a similar result. The effective daily

*Regitine methanesulfonate brand phentolamine methanesulfonate (U.S.P.) CIBA.

Medications were provided by Mr. James G. Smith of Ciba Pharmaceutical Products, Inc.

dose was found to be individual, varying between .25 and 8 mg. Dosages above this level were shown to have increased pharmacological by-effects without additional antihypertensive activity and were abandoned early in the study. A blood pressure response was noted with as little as .25 mg. (2 patients), but the vast majority demonstrated significant reduction only to a daily dosage between 4 and 8 mg.

TABLE 2.—BLOOD PRESSURE RESPONSE TO SYROSINGOPINE WITH RELATION TO SEVERITY

	Smithwick Group							
	I		*II*		*III*		*IV*	
Blood Pressure Response	*No. Pts.*	*%*	*No. Pts.*	*%*	*No. Pts.*	*%*	*No. Pts.*	*%*
Normotension	6	75	17	68	0	0	0	0
Significant Reduction	0	0	1	4	0	0	2	6.9
Slight Reduction	1	12.5	1	4	0	0	16	55.1
No Reduction	1	12.5	6	24	2	100	11	38.0

TABLE 3.—COMPARISON OF BLOOD PRESSURE RESPONSE TO PHARMACOLOGIC BY-EFFECTS WITH SYROSINGOPINE AND RESERPINE IN 34 PATIENTS

	Reserpine .5 mg.		*Syrosingopine 4 mg.*	
	No. Pts.	*%*	*No. Pts.*	*%*
Significant Diastolic Blood Pressure Reduction	15	44	17	50
Pharmacologic By-effects	11	34	4	11.8

The effectiveness of antihypertensive medications is limited by their pharmacologic by-effects and toxicity. Syrosingopine is singularly free of both. The only unmistakable by-effect was nasal congestion, which occurred in 4 patients receiving 4 to 8 mg. daily, and in all 5 patients placed on 12 mg. daily. Fatigue was complained of in 3 patients and mental depression in one. These latter symptoms were not reduplicable upon reinstituting therapy after a brief interruption. Of the group reported, 34 patients had previously received reserpine in a dosage of .5 mg. daily. By-effects in this group comprised approximately 32% and included nightmares, mental depression, fatigue, nausea, and nasal congestion. As indicated in Table 3, the substitution of syrosingopine resulted in a lowering of by-effects to 9% without sacrifice of antihypertensive activity. Toxicity, as determined by repeated hemograms, urinalyses, and hepatic function tests, was not encountered in this study.

The combination of hydralazine with reserpine has an accepted place in antihypertensive therapy. Blood pressure reducing effect of the combination has been shown to be greater than that of either agent used alone. Reserpine has the added effect of preventing tachycardia commonly associated with hydralazine, but the by-effects of both agents are additive with regard to increasing gastrointestinal symptoms, as well as producing nasal congestion. There is a definite therapeutic advantage in combining antihypertensive

medications with the provision that a single drug proves unsatisfactory and that the combination does not increase the incidence of toxicity or uncomfortable pharmacological by-effects. Since the incidence of by-effects with syrosingopine was less than with reserpine, it was logical to combine it with hydralazine in those patients poorly controlled with syrosingopine alone.

Thirty-nine patients inadequately controlled with syrosingopine were maintained on this drug and hydralazine, being gradually titrated to 400 mg. daily when necessary. The additional antihypertensive effect of hydralazine is readily apparent as indicated in Table 4. Since these patients represented a more severe group, the results appear quite significant. The effective daily dosage required varied from 40 to 400 mg. with an average of 200 mg. The incidence of pharmacologic by-effects was increased only slightly and comprised headache (2 patients), nausea (1 patient), and palpitations (1 patient). One patient required discontinuation of therapy because of the appearance of a gastric ulcer, although cause and effect could not be established.

The addition of a second medication possessing similar therapeutic properties raises the question as to whether the effects are due to the combination or merely to the second agent alone. For this reason, an identical placebo was substituted for the syrosingopine and the results reevaluated. This procedure, as indicated in Table 5, demonstrated a definite synergistic action. Comparison studies in this group of patients suggested that the bradycardia produced by syrosingopine was less than that of reserpine; however, this activity is apparently sufficient in most cases to counteract tachycardia produced by hydralazine as indicated by the increased incidence of this complaint upon placebo substitution for syrosingopine in the combination.

The ideal antihypertensive agent does not exist. At present, therapy must be individualized with respect to its ability to reduce elevated blood pressure in a given patient with a maximum of safety and a minimum of undesired by-effects. Syrosingopine alone and in combination with hydralazine has satisfied these requirements in many patients. Dosage requirements depend upon the severity of hyperten-

TABLE 4.—COMPARISON OF THERAPEUTIC RESULTS WITH SYROSINGOPINE ALONE AND IN COMBINATION WITH HYDRALAZINE IN 39 PATIENTS

	Syrosingopine Alone %	*Syrosingopine and Hydralazine* %
Normotension	12.5*	45.3
Significant Blood Pressure Reduction	4.7	37.5
Slight Blood Pressure Reduction	21.9	6.3
No Significant Reduction	60.9	10.9

*5 Patients required hydralazine because of by-effects on large doses of syrosingopine alone.

TABLE 5.—RESULTS OF PLACEBO SUBSTITUTION FOR SYROSINGOPINE IN 20 PATIENTS RECEIVING COMBINATION THERAPY

	Syrosingopine and Hydralazine	*Placebo and Hydralazine*
Significant Blood Pressure Reduction	80%	30%
By-effects Incidence	20%	35%

sion and probably upon other factors as yet unknown. This particular group of patients required a larger daily dose of syrosingopine than has been generally recommended, but this was accomplished with little difficulty.

Summary. The antihypertensive effect of syrosingopine alone and in combination with hydralazine was evaluated in ambulatory hypertensive patients. Placebo substitution for the syrosingopine confirmed its antihypertensive activity when used alone as well as in combination. Effective dosage was found to range from 1 to 8 mg. daily. Overall effectiveness of this medication is similar to that of reserpine, in that hypertension of milder degree responded best. More severe grades of hypertension required the addition of hydralazine. Dosages up to 8 mg. daily resulted in less pharmacologic by-effects than were encountered with 0.5 mg. of reserpine. An increase in these by-effects without comparable increase in therapeutic effect was noted in dosages above 8 mg. daily. The combination of syrosingopine with hydralazine appeared to produce an antihypertensive response similar to the combination of reserpine and hydralazine, but the former appears to possess less tendency to produce sedation and mental depression. Since the treatment of essential hypertension requires a highly individualized approach, it is felt that syrosingopine alone or in combination with hydralazine is of value particularly in those patients experiencing undesirable symptoms due to by-effects of reserpine.

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SUMMARIO IN INTERLINGUA

Le Uso de Syrosingopina (SU-3118) e Hydralazina in le Tractamento de Hypertensivos Ambulante

Le effecto antihypertensive de syrosingopina sol e in combination con hydralazina esseva evalutate in patientes hypertensive ambulante. Le substitution de placebo pro syrosingopina confirmava su activitate antihypertensive quando le droga esseva usate sol e etiam quando illo esseva usate in combination. Esseva trovate que le dosage efficace variava inter 1 e 8 mg per die. Le efficacia general de iste medication es simile a illo de reserpina in tanto que hypertension de leve grados respondeva le melio. Grados plus sever de hypertension requireva le addition de hydralazina. Dosages de usque a 8 mg per die resultava in plus basse effectos pharmacologic lateral que 0,5 mg de reserpina. Un augmento de iste effectos lateral sin comparabile augmento del effecto therapeutic esseva notate in le uso de doses de plus que 8 mg per die. Le combina-

tion de syrosingopina con hydralazina pareva producer un responsa antihypertensive simile al combination de reserpina con hydralazina, sed le prime possede apparentemente minus le tendentia de producer sedation e depression mental. Viste que le tractamento de hypertension essential require un altemente individualistate methodologia, le disponibilitate de syrosingopina es un addition benvenite al medicationes antihypertensive. Usate sol o in combination illo pare esser de valor particularmente in patientes in qui le effectos lateral de reserpina constitue symptomas de character indesirabile.

SUMMARIO IN INTERLINGUA

(See page 144 for original article)

Concentration Osmolar del Urina: Un Medio pro le Evalutation de Precoce Alterationes del Function Renal in Hypertension Essential

1. Un total de 45 observationes esseva facite in 36 patientes hypertensive qui demonstrava normal functiones renal secundo le usual tests (nitrogeno de urea sanguinee, concentration de Fishberg, phenolsulfonphthaleina, urogramma intravenose, e clearance de creatinina). Le concentration osmolar del urina sub conditiones hydropenic in 32 de 36 patientes esseva minus que 800 mOsm per L, lo que indicava un defecto del capacitate concentratori del renes.

2. Le prime detegibile injuria del function renal in hypertension essential pare occurrer in le capacitate del renes de concentrar urina sub conditiones hydropenic.

3. Le determination del concentration osmolar del urina es un simple e rapide test de valor in observar le function renal ab le puncto de vista prognostic e in evalutar le efficacia del programma therapeutic instituite in hypertension essential.

INTRAVENOUS MECAMYLAMINE (INVERSINE)* AS A MEANS OF DETERMINING THE EFFECTIVE ORAL DOSAGE

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The introduction of chlorothiazide, hydrochlorothiazide and related compounds as adjuncts in the treatment of hypertension has permitted better control of the disease in many patients. However, in our experience, the severe hypertensive often requires ganglionic blocking agents, in addition to other drugs, for a satisfactory response. Side effects with ganglionic blocking agents are common. This necessitates a slow and careful progression of the dosage. It may require a period of 8 to 12 weeks, or longer, before a satisfactory therapeutic response becomes evident. With most hypertensives, such a delay may not prove harmful but in those with malignant or accelerated hypertension, this prolonged period may result in irreversible renal damage and uremia.

The use of parenteral reserpine, in combination with an oral thiazide, has been quite successful in treating hypertension in semi-emergent situations. However, when oral medication is substituted for the parenteral form, the blood pressure usually returns to severe hypertensive ranges within a few weeks. To avoid this, it is sometimes customary to change to an oral ganglionic blocking agent. The problem of dosage confronts the physician, and before an adequate oral dose may be determined by the necessary method of trial and error, irreversible renal damage may have occurred. The procedure outlined herein may avoid this series of events.

Mecamylamine was introduced as a therapeutic agent in 1955 (Freis[1]). It was apparent that its absorption from the gastrointestinal tract was more predictable than other previously used ganglionic blocking drugs. Smirk and McQueen[2], in fact, studied the oral and intravenous effect of similar amounts of mecamylamine, and comparable decreases in blood pressure were found to occur. Therefore, we felt justified in using this drug intravenously in the hope that the minimal oral dose, with which a given hypotensive effect might be expected, could

*The parenteral mecamylamine was supplied by Dr. John C. Richards of Merck, Sharp and Dohme.

be determined. If this could be accomplished, a period of delay between initiation of oral therapy and a satisfactory response could be avoided.

Materials and Methods. Eleven patients were selected from the hypertension clinic and the wards of the Los Angeles County Hospital for our study. All of these patients suffered from severe hypertension and all demonstrated some complication of hypertension either in the form of grade III or IV Keith-Wagener retinopathy, left ventricular hypertrophy, cerebrovascular accident or renal damage (Table 1). Supine and standing control blood pressures were determined both in the clinic and during a period of observation in the hospital. These are represented as average values in Table 2.

A solution of mecamylamine was added to 5% glucose in water in the ratio of 1 mg. per 5 ml. The rate of the intravenous infusion was adjusted to approximately 0.5 mg. of mecamylamine per minute. Supine and standing blood pressures were determined every 5 minutes. All patients were hospitalized for

TABLE 1.—PERTINENT DATA ON THE HYPERTENSIVE PATIENTS STUDIED.

Patient	*Age*	*Sex*	*Race*	*LVH*	*CVA*	*Serum urea*	*Urine*	*Funduscopic Grade*
L.C.J.	51	M	N	Yes	No	15	Normal	grade II
E.Y.	52	F	C	Yes	Yes	21	Albumin	grade III
P.A.	43	M	N	Yes	No	30	Albumin	grade III
N.H.	26	M	N	Yes	No	15	Albumin	grade III
H.S.	56	M	N	Yes	No	43	Albumin	grade IV
B.H.	41	F	N	Yes	No	31	Albumin	grade III
J.M.	61	M	C	Yes	No	17	Normal	grade III
A.W.	54	M	N	Yes	No	84	Albumin	grade III
A.J.	51	M	N	Yes	No	39	Albumin	grade II
W.M.	51	M	N	Yes	No	10	Albumin	grade II
M.L.	44	F	N	Yes	No	25	Albumin	grade III

TABLE 2.—AVERAGE BLOOD PRESSURES BEFORE INTRAVENOUS MECAMYLAMINE.

	Average B/P			*Number of Determinations*	
	Supine	*Standing*	*Period of observation*	*Supine*	*Standing*
L.C.J.	189/139	178/124	9 days	14	13
L.C.J.	205/132	193/137	3 mos.	9	4
E.Y.	220/142	200/136	2 mos.	7	6
P.A.	208/136	195/131	3 mos.	229	23
N.H.	169/119	151/120	3 mos.	11	6
H.S.	215/142	162/106	7 days	17	4
B.H.	242/134	208/126	7 mos.	9	9
J.M.	193/112	200/115	4 mos.	71	2
A.W.	185/140	188/140	10 days	27	2
A.J.	197/143	190/138	1 mo.	91	86
W.M.	217/137	184/131	8 mos.	25	14
M.L.	233/136	216/130	3 mos.	6	6

this procedure. A single initial study was performed in the semirecumbent position (patient LCJ). All subsequent studies were performed while measuring the blood pressure in both the supine and standing positions. The blood pressure response in the standing position was used to determine the end point of the infusion. It was planned to terminate the infusion when a standing pressure of 140/90 was reached. It was further decided that a maximum of 90 mg. of mecamylamine would be given. After the infusion was terminated, the blood pressure was checked frequently during the night.

Following 6 such procedures, performed on 5 patients (W.M., LCJ., A.J., B.H., and M.L.), the blood pressure was allowed to return to distinctly high levels before oral mecamylamine was given. In the remainder, oral mecamylamine was given the day following the infusion, before hypertensive levels had returned. The oral dose of mecamylamine was similar to the total intravenous dose in each instance. The patients were then followed for a variable period of time with supine and standing blood pressures recorded at frequent intervals.

Results. Figure 1 illustrates the blood pressure changes recorded in one patient during the intravenous administration of mecamylamine and immediately after the procedure was discontinued. It is to be noted, that the standing pressures dropped much more than did the supine pressures. In addition, there was a fall to an even lower level after cessation of the infusion. A slow return of the blood pressure toward its previous level took place as the period of observation was extended.

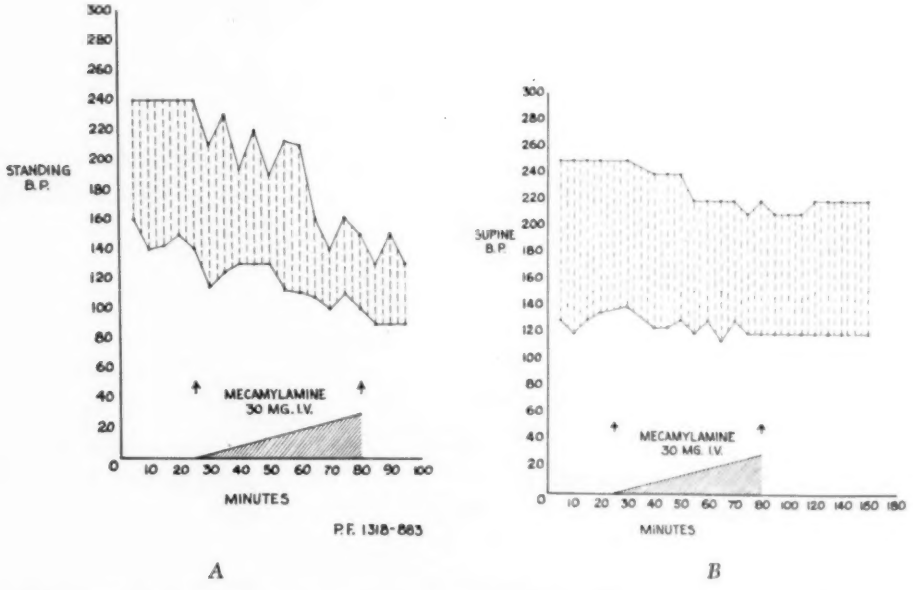

Fig. 1*A* and *B*.—A graph of the blood pressure response to intravenous mecamylamine in the standing (*A*) and supine (*B*) position illustrating the difficulty in arriving at an end point when the supine blood pressures are used alone.

Table 3 presents the amount of intravenous mecamylamine given, the blood pressure responses and the duration of the infusion in all subjects studied. One patient of the 11 failed to respond to the maximum dosage of 90 mg. of intravenous mecamylamine. Only one of the remaining patients (A.W.) did not reach normotensive levels during the in-

fusion, but a significant drop in blood pressure did occur. In the remainder, the blood pressure reached normotensive values. The dose required to lower the blood pressure varied widely but our average corresponded closely to that found by others (Smirk and McQueen[2]). The patient who failed to respond to 90 mg. of mecamylamine died several days later of a cerebral hemorrhage.

Table 4 compares the blood pressure before the intravenous mecamylamine and the degree of control of the hyper-

TABLE 3.—BLOOD PRESSURE LEVELS AT THE TIME WHEN THE INFUSION OF MECAMYLAMINE WAS DISCONTINUED, AMOUNT OF DRUG INFUSED AND DURATION OF INFUSION.

	Supine	*Standing*	*Mg.*	*Min.*
L.C.J.	——	*140/100	20	64
L.C.J.	205/128	90/80	12	35
E.Y.	200/130	110/96	26	92
N.H.	136/110	106/94	34	65
H.S.	170/110	98/80	15	20
B.H.	220/120	120/90	30	60
I.M.	180/100	140/94	30	70
A.W.	148/118	130/110	90	200
A.J.	180/140	110/80	57	120
W.M.	180/120	120/90	30	30
M.L.	250/164	90/70	20	30
†P.A.	228/140	222/130	90	120

*Semirecumbent position only
†Patient failed to respond.

TABLE 4.—COMPARISON OF THE AVERAGE BLOOD PRESSURES BEFORE THE INTRAVENOUS MECAMYLAMINE AND AFTER ORAL MECAMYLAMINE WAS STARTED IN THE DOSAGE INDICATED BY THE INTRAVENOUS TEST.

	Before Mecamylamine		*After Mecamylamine*			
Patient	*Supine*	*Standing*	*Supine*	*Standing*	*Days Observed*	*Number of Determinations*
W.M.	217/137	184/131	171/113	132/108	8 days	39
E.Y.	220/142	200/136	212/102	124/83	5 days	11
M.L.	233/136	216/130	195/113	150/90	11 days	34
A.J.	197/143	190/138	180/126	146/104	8 days	16
B.H.	242/134	208/126	207/115	116/71	12 days	73
L.C.J.	205/132	193/137	169/115	151/108	7 days	29
I.M.	193/112	200/115	160/103	134/92	3 days	15
L.C.J.	189/139	178/128	178/115	150/92	6 days	9
H.S.	215/142	162/106	153/97	149/98	9 days	23
N.H.	169/119	151/120	174/109	115/91	3 days	15
A.W.	185/140	188/140	160/114	159/108	16 days	76

tension by a similar oral amount of the drug. Initially the oral mecamylamine was given once daily, as it was found that for 24 to 72 hours after the intravenous infusion lability of the blood pressure existed. Subsequently the mecamylamine was given every 12 hours. A satisfactory response to the oral dosage, as ascertained by the intravenous infusion, was evident in each instance.

One patient (L.C.J.) was given intravenous mecamylamine on two widely spaced occasions. Only the semirecumbent blood pressure was followed during the first procedure, whereas, both the supine and standing pressures were taken on the second occasion. The results (Table 3) revealed, as expected, that a smaller amount of mecamylamine was needed to produce the desired effect, when the standing blood pressure was used as a guide.

Discussion. The fact that the supine blood pressure did not drop precipitously served as a safety measure to combat severe postural hypotension. If, however, only supine blood pressures were used to determine the end point of the infusion, disabling and prolonged hypotension often resulted. When the standing blood pressure response was used as the indication to stop the infusion, no severe reactions took place. On several occasions the patients felt faint during the infusion but this was relieved immediately by allowing them to recline. Careful observation during the intravenous infusion of mecamylamine was required as the standing blood pressure often fell rather rapidly to levels below those anticipated. When the standing blood pressure was checked every 5 minutes throughout the procedure, no severe reactions occurred.

It should be emphasized, that for a 1- to 3-day period after the infusion only one daily dose of oral mecamylamine should be given. Following this period, it usually was necessary to give the indicated dosage every 12 hours.

Those patients with an elevated serum urea usually had a further elevation with any major drop in blood pressure. They should be observed in the hospital until stabilization of the serum urea has occurred and it has been ascertained that uremia has not been precipitated.

It is advisable to administer other medications, which are to be used as adjunctive antihypertensive therapy, for several days preceding the intravenous infusion as these medications may change the requirements for mecamylamine.

Conclusions. 1) The blood pressure drop found with intravenously administered mecamylamine correlates well with the oral dosage required to produce a satisfactory antihypertensive response. 2) During the first 1 to 3 days after the intravenous procedure only a single oral dose of mecamylamine should be given. Following this period it usually is necessary to give the indicated dosage every 12 hours. 3) The standing blood pressure should be used as a guide for the termination of the intravenous infusion of mecamylamine, as prolonged and severe hypotension may otherwise result.

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(Interlingua on page 174)

ASYMPTOMATIC BACILLURIA IN SIXTY-EIGHT DIABETIC PATIENTS

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It has been our experience that not infrequently diabetic patients entering the hospital are found unexpectedly to have positive urine cultures despite lack of symptoms of urinary tract infection. Furthermore, following appropriate treatment for the asymptomatic bacilluria, considerable decrease in the daily requirement for insulin often occurs. These findings suggested that the bacilluria is of importance clinically and the question arose as to what features characterized the diabetic patient who enters the hospital with asymptomatic bacilluria. Consequently, a study was carried out to determine the incidence of this condition and the type of patient concerned.

According to Kass[5], among persons in the general population, pyelonephritis is second in frequency only to respiratory infections. Beeson[2] states that urinary tract infections are three to four times as common in diabetics as in nondiabetics of comparable age. As possible reasons for this, he suggests increased susceptibility to infections, enhanced growth of bacteria in sugar-containing urine and relatively frequent catheterization. Beeson considers an active infection to be present when cultures reveal more than 10,000 bacteria per ml. of urine. Other investigators (Kass[5], Kass and Scheiderman[6]) consider significant bacilluria to be present when there are more than 100,000 bacteria per ml. of urine. There are numerous intermediary classifications.

Among 1196 necropsies from the general population, Brod[3] found clinically unrecognized chronic pyelonephritis in 6.18%. He commented that in diagnosing this condition little is to be gained from the patient's history, clinical examination or routine laboratory tests. The total number of diabetic patients necropsied at the New England Deaconess Hospital, Department of Pathology, 1950 through 1956, was 414. Of these, 169 or 40.8%, gave evidence of urinary tract inflammation (Legg[7]). In the Outpatient Department of the Boston City Hospital, Kass found asymptomatic bacilluria to be present in 18% of 57 diabetic females and 5% of 37 diabetic males.

In a study of 52 diabetic patients at the New England Deaconess Hospital, Barnard, Story and Root[1] found the most frequent infecting organism to be *Aerobacter sp.* On the other hand, Brod[3] in the study previously mentioned, reported coliform bacilli as the cause for 45% of the infections. In agreement with this, Hyman[4] observed coliform bacilli to be the infective agent in 80% of uncomplicated cases.

Plan of Study. During the period of study, all diabetic patients admitted to one section of the Joslin Clinic Service of the New England Deaconess Hospital submitted "clean" voided specimens of urine for culture, colony count, sensitivity studies, and determination of sugar content. Male patients submitted midstream clean voided specimens. Females were cleansed with tincture of Zephiran, 1:1000, and specimens collected in a sterile container. Samples from specimens were incubated within one hour after voiding.

The percentage of sugar in urine was determined by the method described by Sumner[10,11]. The blood sugar of the study patients was determined by the Somogyi-

Nelson method for true glucose (Nelson[8], Sumner[11]).

Excluded from the study were patients who had symptoms referable to the genitourinary tract, enlargement of the prostate, cystocele, paresis of the urinary bladder or who had previously been catheterized or subjected to instrumentation. Patients confined to bed for 2 or more days prior to hospital entry were reviewed separately. In study patients with skin ulcers or other open lesions including surgical wounds and in those patients raising sputum, cultures were made from material from these lesions or from the sputum.

Results. During the period of investigation, 68 patients with diabetes entered the hospital who from history or on physical examination gave no evidence of infections or other abnormalities of the genitourinary tract. Of these, 23 or 34% were found on examination to have a bacterial colony count greater than 100,000 per ml. of urine. Of the 23, 17 had been confined to bed for 2 or more days prior to entry. There were 22 male and 46 female patients. Among the 23 patients with colony counts greater than 100,000 per ml., 19 were females and 4 were males.

From Table 1, it is evident that 17 or 68% of the 25 patients who had been confined to bed had colony counts greater than 100,000 per ml. whereas only 6, or 14%, of 43 patients who had been up and about prior to admission, had colony counts in this high range.

Fever was present in 4 of the 68 patients included in the study but in none of these was urinary tract infection considered to be the cause of the elevation of temperature.

It is noteworthy that the finding of leukocytes in the urinary sediment, distributed as scattered cells or in clumps, was unreliable in predicting bacilluria. Of 23 cases with asymptomatic bacilluria, counts greater than 100,000 per ml., only 2 had clumps of white blood cells in the sediment and there were 8 with less than 5 leukocytes per high power field of the microscope (Table 2).

We could not substantiate the statement that the amount of sugar in the urine is an important factor in favoring bacilluria. Of the 23 patients with bacilluria greater than 100,000 per ml., 8 gave negative tests for sugar in the urine and only 5 had greater than 2% of sugar (Table 3). In the course of

TABLE 1.—COLONY COUNTS PER ML. OF URINE IN 68 "ASYMPTOMATIC" ADMISSIONS

		$>10^5$		50,000 to	25,000 to	10,000 to	2000 to		
Physical activity	*No.*	*No.*	*%*	80,000	40,000	23,000	5000	<2000	*No growth*
Confined to bed before entry	25	17	68	1	1	2	1	1	2
Not confined before entry	43	6	17	1	3	3	6	6	29
Total	68								

TABLE 2.—FREQUENCY OF LEUKOCYTES AND CLUMPS IN SEDIMENTS OF 23 CASES WITH BACILLURIA $>10^5$

Leukocytes	0	0–5	5–15	10–30	25–70	75–100
Cases	1	8	7	2	4	1
Clumps	0	0	0	0	1	1

TABLE 3.—SUGAR CONCENTRATION IN URINE IN CASES WITH BACILLURIA $>10^5$

Gm. %	3–7	1–2	0.1–0.7	none
No. cases	5	5	5	8

the study it was found that often patients with considerable amounts of sugar in the urine gave negative cultures.

Of the 23 patients with asymptomatic bacilluria and colony counts greater than 100,000 per ml., 10 were overweight. Only 5 had a systolic blood pressure over 180 mm. and a diastolic pressure over 90 mm. Nine patients took more than 30 units of insulin a day and 3 were receiving oral hypoglycemic agents. The duration of diabetes varied from 1 to 30 years with a mean of 13.3 years. Eight patients had had poor control of diabetes prior to entry. These 8 patients paid relatively little attention to diet, tested the urine only occasionally and visited a physician irregularly.

In Table 4 are given certain relevant data. It will be noted that protein was present in the urine in a majority of patients.

In certain instances the blood glucose values do not appear consistent with the amount of sugar in the urine. In large part this was due to the fact that at times there was an interval of a few hours between the time of collecting the urine specimen and the drawing of blood for sugar determination.

For various reasons, 6 of the 23 patients had been given antibiotics prior to entering the hospital. Of these, 2 had colony counts greater than 100,000, 1 had 40,000 per ml. and 2 had negative cultures. The sixth patient who had been confined to bed prior to admission, had a count of 3,000 per ml. of urine.

Nine of the 23 patients with bacilluria of 100,000 per ml. or greater, had

TABLE 4.—OBSERVATIONS IN 23 CASES WITH BACILLURIA $>10^5$ AT THE TIME OF ADMISSION TO THE HOSPITAL.

Urine sugar gm.%	*Blood glucose mg./100 ml.*	*Urinary sediment findings per HPF of microscope*			*Albumin mg./100 ml.*	*NPN mg./100 ml.*
		WBC	*Casts*	*Clumps*		
7.0	118	30–50	0	0	20	17
6.0	–	0–3	rare	0	56	30
5.0	–	5–10	0	0	0	31
3.6	266	60–70	0	0	25	30
3.1	305	5–12	few	0	100	38
2.0	–	0–3	0	0	0	33
1.7	482	0–3	0–4	0	50	43
1.6	341	6–12	few	0	100	51
1.6	386	8–10	few	0	700	54
1.4	245	40–60	0	0	20	28
0.7	200	15–25	occ.	0	250	90
0.6	265	1–5	0	0	0	—
0.6	180	0	0	0	0	33
0.1	122	0–3	0	0	20	31
0.1	–	4–10	0	0	20	36
0	85	25–30	0	Many	18	32
0	58	10–20	0–2	0	20	40
0	142	75–100	0	occ.	20	36
0	251	2–3	0	0	35	42
0	122	15–30	occ.	0	520	60
0	133	7–10	0	0	20	34
0	130	8–10	0	0	20	26
0	167	0–3	0	0	0	37

TABLE 5.—INCIDENCE OF INFECTING ORGANISM AND FREQUENCY OF RESISTANCE TO ANTIBIOTICS IN 23 CASES WITH BACILLURIA $>10^5$

		No. of cases in which organism was resistant to antimicrobial agents.										
Infecting organism	No. cases infected	Albamycin	Penicillin	Aureomycin	Streptomycin	Chloromycetin	Terramycin	Tetracycline	Erythromycin	Furadantin	Bacitracin	Neomycin
E. coli	9	9	9	4	3	0	1	2	8	0	9	0
B. proteus	8	4	6	6	3	4	7	7	8	6	8	0
Aerobacter sp.	5	3	5	1	3	0	4	3	5	1	5	0
Staph. alb., coag. neg.	5	0	4	3	5	2	5	4	2	0	2	0
Strept. anhemol.	3	0	0	1	2	0	3	2	1	0	0	2
Strept. viridans	3	0	0	0	2	0	0	0	0	0	0	2
Strept. hemol.	1	0	0	0	1	0	0	0	0	0	0	1
Coliform	1	1	1	1	0	0	0	0	1	0	1	0
Pseudomonas	1	1	1	1	1	1	1	1	1	1	1	0
Total	36	18	26	17	20	7	21	19	26	8	26	5

TABLE 6.—INCIDENCE OF INFECTING ORGANISM AND FREQUENCY OF RESISTANCE TO ANTIBIOTICS IN 12 CASES OF BACILLURIA WITH COLONY COUNTS OF 10,000 TO 80,000 PER ML. OF URINE.

		No. of cases in which organism was resistant to antimicrobial agents.										
Infecting organism	No. cases infected	Albamycin	Penicillin	Aureomycin	Streptomycin	Chloromycetin	Terramycin	Tetracycline	Erythromycin	Furadantin	Bacitracin	Neomycin
Strept. hemol.	4	1	1	2	3	2	2	3	2	1	1	1
E. coli	3	2	3	1	1	0	2	1	2	0	3	0
B. proteus	2	1	0	2	0	0	2	1	2	1	2	0
Coliform	2	2	2	1	2	1	2	1	2	0	2	0
Staph. alb., coag. neg.	1	0	0	1	0	0	1	1	1	0	1	0
Pseudomonas	1	1	1	1	1	1	1	1	1	1	1	0
Strept. anhemol.	1	0	0	0	1	0	0	0	0	0	0	1
Total	14	6	7	8	8	4	10	8	10	3	10	2

more than one organism in the urine. The frequency of occurrence of various organisms and of their resistance to antimicrobial agents, is shown in Table 5.

In 12 cases colony counts between 10,000 and 80,000 per ml. were obtained. Data regarding these are shown in Table 6, in which are given the types of infecting organisms and their resistance to antimicrobial agents.

Open foot lesions were a major cause for hospital entry in 15 patients; in 5 of these the colony count was greater than 100,000 per ml. However, the organisms cultured from the skin lesions and those obtained from the urine were different in all instances. Three patients with bacilluria of 100,000 per ml., or greater, had organisms cultured from other parts of the body which were identical with those present in the urine. In one case *Streptococcus hemolyticus* was cultured from both sputum and urine. In another patient *E. coli* was cultured from a draining chest fistula and the urine. A third patient had coliform organisms cultured from gallbladder and urine. In all 3 cases, the organisms which were isolated were resistant to the same antimicrobial agents.

Renal function studies were done in all 68 cases. The results showed no correlation with the frequency of urinary tract infections.

There were 23 patients with diabetic retinopathy. Of these, 6 had colony counts greater than 100,000 per ml.

Summary and Conclusions. 1. Sixty-eight patients with no indication of urinary tract disease from history or physical examination were studied on admission to the hospital. Of these, 23 or 34% were found to have asymptomatic bacilluria with colony counts greater than 100,000 ml. of urine. Sixty-eight per cent of patients confined to bed prior to entry had bacilluria to this extent as compared to 14% among patients not confined to bed prior to hospital admission.

2. Findings in the urinary sediment were of little value in indicating those patients with asymptomatic bacilluria of significant degree.

3. The sugar content of the urine showed no consistent correlation with the frequency of bacilluria or the number of organisms cultured.

4. Organisms causing bacilluria to the extent of 100,000 colonies per ml. or greater were most frequently *E. coli, B. proteus, Staphylococcus albus* and *Aerobacter sp.*

5. Bacilluria greater than 100,000 per ml. was present in 41% of females and 18% of males. Asymptomatic bacilluria was definitely more common in diabetic patients who had been confined to bed prior to admission than in those who had been ambulatory.

6. In conclusion, among diabetic patients entering a hospital for various reasons, there is a significant percentage with asymptomatic bacilluria of 100,000 colonies per ml. despite the absence of symptoms referable to urinary tract infection. Only by routine cultures and colony count carried out with a "clean" voided specimen of urine can such bacilluria be found.

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SUMMARIO IN INTERLINGUA

Bacilluria Asymptomatic in Sexanta-Octo Patientes Diabetic

1. Sextanta-octo diabeticos sin evidentia de morbo del vias urinari in lor historias clinic o in le examine physic esseva studiate per medio de un technica de culturation urinari al tempore de lor admission al hospital. Esseva constatate que 23 de illes, *i.e.* 34%, habeva bacilluria asymptomatic con numerationes de colonias de supra 100.000 per ml de urina. Sexanta-octo pro cento del patientes qui habeva essite allectate ante lor hospitalisation habeva bacilluria del grado indicate, in comparation con 14% del patientes non allectate ante lor hospitalisation.

2. Le constatationes in le sedimento urinari esseva de pauc valor pro le recognition del patientes con grados significative de bacilluria asymptomatic.

3. Le contento de sucro in le urina revelava nulle uniforme correlation con le presentia de bacilluria o le numero del organismos culturate.

4. Le organismos le plus frequentemente responsabile pro bacilluria de 100.000 colonias per ml o plus esseva *Escherichia coli, B. proteus, Staphylococcus albus,* e *Aerobacter sp.*

5. Bacilluria de plus que 100.000 colonias per ml esseva constatate in 41% del femininas e 18% del masculos. Bacilluria asymptomatic esseva definitemente plus commun in patientes diabetic qui habeva essite allectate ante lor hospitalisation que in illes qui habeva essite ambulatori.

6. In conclusion: Inter le patientes diabetic qui es hospitalisate pro varie rationes, il occurre un procentage significative de subjectos con bacilluria asymptomatic de 100.000 colonias per ml in despecto del absentia de symptomas que pote esser attribuite a infection del vias urinari. Il es solmente per medio del culturation routinari con numeration del colonias super le base de non contaminate specimens de urina que tal bacilluria pote esser trovate.

COMPARATIVE EFFECTS ON URINARY ELECTROLYTE EXCRETION FOLLOWING TWO BENZOTHIADIAZINE DIURETICS, FLUMETHIAZIDE AND CHLOROTHIAZIDE

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The purpose of this report is to present a comparison of the electrolyte excretion effects of two similar benzothiadiazine diuretic agents, flumethiazide and chlorothiazide.

Materials and Methods. Ten patients (cardiacs with mild edema) under controlled metabolic conditions were each given single doses of 1.0 gm. of chlorothiazide and 1.0 gm. of flumethiazide at 5- to 7-day intervals after their return to control state. Five patients were given chlorothiazide first, and the other 5 were given flumethiazide first. Each patient received both drugs. Observations on the 24-hour urinary output were made for sodium, potassium, bicarbonate, chloride, pH, and volume in the control state and on the day the drug was given.

Results. A. SODIUM. The data as illustrated in Table 1 reveal that the average increase in urinary sodium over control after 1.0 gm. of flumethiazide is 40 mEq. per 24 hours, as compared with a 44 mEq. increase produced by chlorothiazide 1.0 gm. This does not represent a statistically significant difference in the amount of increase between the two drugs.

B. CHLORIDE. Table 1 also reveals the comparative average increase in chloride excretion over a 24-hour period after separate doses of flumethiazide 1.0 gm. and chlorothiazide 1.0 gm. Flumethiazide produced an increase of 33 mEq. per 24 hours and chlorothiazide produced an increase of 38 mEq. per 24 hours. There was no significant difference between the response to the two drugs.

C. POTASSIUM. A greater increase in potassium (18 mEq. per 24 hours) was observed with chlorothiazide 1.0 gm. in comparison with that of flumethiazide 1.0 gm. (9 mEq. per 24 hours). Although the increased excretion is significant for each of the drugs, the degree of increase is less with flumethiazide than with chlorothiazide.

D. BICARBONATE. Flumethiazide, 1.0 gm., elicited significantly less response in bicarbonate excretion (6.0 mEq.) over a 24-hour period than did chlorothiazide, 1.0 gm. (15.4 mEq.).

E. pH. Flumethiazide produced less increase in pH (0.5 pH units) over the control than did chlorothiazide (2.0 pH units). The increase in pH with chlorothiazide is statistically significant but that obtained with flumethiazide is not.

F. VOLUME. The increase in urine volume compared to the control, after receiving flumethiazide, 1.0 gm., was 0.3 L. per 24 hours. Chlorothiazide, 1.0 gm., produced an increase of 0.4 L. per 24 hours. This is not a significant difference. Both drugs produced a statistically significant increase in volume per 24 hours.

Conclusions and Summary. The administration of 1-gm. doses of flumethiazide and chlorothiazide under controlled conditions resulted in a significant increase in potassium excretion for both drugs, but there was not a sig-

nificant difference between the amount of the increase when the two were compared. There was less increase in pH and bicarbonate excretion with flumethiazide than with chlorothiazide. With flumethiazide the increase in pH and bicarbonate was not significant, while with chlorothiazide the increases were of significant magnitude.

For these reasons flumethiazide may be said to promote a less complicated natriuretic effect than does chlorothiazide when the two drugs are given in equal doses.

TABLE 1.—COMPARATIVE EFFECT OF URINARY ELECTROLYTES FOLLOWING FLUMETHIAZIDE AND CHLOROTHIAZIDE

(Average values for 10 patients)

	Flumethiazide 1.0 gm.			*Chlorothiazide 1.0 gm.*			
	C	*D*	*I*	*C*	*D*	*I*	
Sodium (mEq./24 hrs.)	45	85	40	44	88	44	
P value[F]			<.001			<.001	
*							N.S.
Potassium (mEq./24 hrs.)	33	42	9	34	51	18	
P value			<.05			<.01	
*							.05
Bicarbonate (mEq./24 hrs.)	1.0	7.0	6.0	1.1	16.5	15.4	
P value			<.05			<.01	
*							.05
Chloride (mEq./24 hrs.)	35	68	33	34	72	38	
P value			<.001			<.001	
*							N.S.
pH	5.2	5.7	0.5	5.2	7.2	2.0	
P value			<.1			<.01	
*							.05
Volume (L./24 hrs.)	3.1	3.4	0.3	3.1	3.5	0.4	
P value			<.05			<.05	
*							N.S.

Key:
C = Control Excretion D = Drug Excretion I = Increase in excretion
F_P value = Derived from Student's "t" test.

* = Significance of difference between drugs.

SUMMARIO IN INTERLINGUA

Studio Comparative del Effectos Exercite Super le Excretion Urinari de Electrolytos per Duo Diureticos Benzothiadizinic, Flumethiazido e Chlorothiazido

Le administration de doses de 1 g de flumethiazido e chlorothiazido sub conditiones controlate resultava in un augmento significative del excretion de kalium in ambe casos, e quando le duo esseva comparate, nulle significative differentia inter le quantitate del augmentos esseva notate. Le augmento de pH e de bicarbonato excernite esseva minus marcate post flumethiazido que post chlorothiazido. Post flumethiazido le augmento de pH e de bicarbonato non esseva significative, durante que in le caso de chlorothiazido, ille augmentos esseva de magnitudes significative.

A causa de iste rationes il es possibile asserer que flumethiazido promove un minus complicate effecto natriuretic que chlorothiazido quando le duo drogas es administrate in doses equal.

POTENTIATION AND STABILIZATION OF AORTIC STRIP PRESSOR ASSAY BY PLASMA AND HYDROCORTISONE: ROUTINE USE IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA*

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Spirally cut strips of rabbit aorta contract in the presence of epinephrine and norepinephrine and certain other substances (Furchgott and Bhadrakom[2], Helmer[4,5]) and can be used in the diagnosis of pheochromocytoma (Helmer[5]). Potassium chloride and unidentified substances in urine and plasma increase the sensitivity of the response (Helmer[4,5]). Also, iproniazid, an amine oxidase inhibitor, is known to increase the response to histamine and hydroxytyramine, and in lesser degree to epinephrine and norepinephrine (Helmer[5]). We have potentiated the reaction of the rabbit aorta strip preparation and raised its sensitivity by the addition of hydrocortisone and plasma to the bath.

Method. A spiral strip of aorta, 5 mm. by 45 mm., from a 5- to 8-pound rabbit is mounted in approximately 15 ml. of Krebs solution (Furchgott and Bhadrakom[2], Helmer[5]). For urine pressor assays a modified Krebs solution was used (Table 1). Oxygen and carbon dioxide, 9:1, are bubbled slowly through the bath and the reservoir of Krebs solution and the pH maintained at approximately 7.4. The strip is allowed to equilibrate in the solution for 2 to 3 hours. A recording device magnifies contractions 10-fold as the drum rotates at a rate of 5 mm. per minute. Near maximal responses develop during this time interval as judged by occasional tests with epinephrine-HCl standards (Parke Davis Adrenalin Hydrochloride 1:1000 diluted with .01 HCl to yield concentrations of 20 and 100 gamma per liter). One-tenth milliliter of the 20 gamma per liter standard contains .002 gamma epinephrine and is usually sufficient for a recurring measurable response.

TABLE 1.—MODIFIED KREBS BATH SOLUTION

NaCl	6.923	gm./L.
KCl	.349	gm./L.
$CaCl_2$	.282	gm./L.
KH_2PO_4	.159	gm./L.
$MgSO_4$	.138	gm./L.
$NaHCO_3$	2.212	gm./L.
Human plasma	13.5	ml./L.*
Glucose	2.0	gm./L.*
Hydrocortisone (alcohol, Merck)	12.5	mg./L.*

*Added just before use; remainder prepared in 19.5 L. batches and refrigerated.

Three minutes after the addition of a standard or a test substance, the strip is washed with modified Krebs solution and allowed to return to the baseline. An initial titration curve is recorded by using increasing amounts of epinephrine. Test substances, plasma or urine, are then added in dilutions or quantities sufficient to produce contraction within the range of responses to standard solutions. The standard titration curve is repeated at intervals

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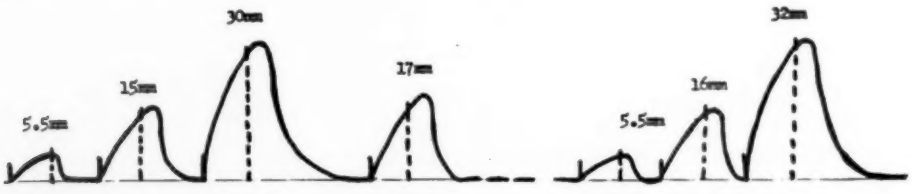
of 3 hours. The height of contractions at 2 or 3 minutes after the addition of the standards are determined and correlated to the respective quantities of epinephrine added. The height of contractions of the unknowns are similarly determined. By interpolating the height of contractions of the unknowns within a series of averaged standard curves, the pressor content of the unknowns is determined and expressed as gamma epinephrine equivalents (g.e.e.) per liter. Sample responses and calculations are shown in Fig. 1.

The urine or plasma for testing was brought to pH 3.5 with concentrated hydrochloric acid and kept refrigerated.

added to 15 ml. of bath solution produced maximum plasma potentiation.

Hydrocortisone, 0.2 mg. in 15 ml. of the modified Krebs solution to which 0.2 ml. of plasma had been added, further potentiated the response to epinephrine (Table 2). Four times this amount of hydrocortisone had not produced a further increase on previous experiment. Hydrocortisone also altered the character of the response. When first attached the muscle strip did not relax as quickly as in Krebs-bicarbonate-



GAMMA OF EPINEPHRINE/LITER OF STANDARD	MILLIMETER RISE AT THREE MINUTES	CALCULATIONS
20	5.5) av. 5.5) 5.5	.1cc Urine A rose to 17mm at three minutes
60	15.0) av. 16.0) 15.5	Therefore: $\frac{(17-15.5)}{(31-15.5)} \times (100-60) + 60 =$ 64g.e.e./L.
100	30.0) av. 32.0) 31.0	If 24 hour urine volume=1.2L. 64 x 1.2 = 77 g.e.e./24 hours.

Fig. 1.—Shows a series of standardization responses (titration curve) obtained initially and again in 3 hours and the calculation of results obtained with a sample of urine.

Results. A. EFFECTS OF URINE, PLASMA AND HYDROCORTISONE UPON THE MUSCLE STRIP. The addition of urine, 0.1 ml., produced unpredictable alterations in the sensitivity and the performance of the muscle strip in response to standard solutions of epinephrine. Plasma definitely potentiated the response to epinephrine without altering its character but did not cancel the erratic behavior of the strip when urine was added. Two-tenths milliliter of plasma glucose solution alone. Also, the contraction and the relaxation were slowed as with the addition of KCl (Furchgott and Bhadrakom[2]). Hydrocortisone however stabilized the response so that urine no longer erratically altered the performance of the muscle strip. Hydrocortisone eliminated the dampening effect of large contractions upon subsequent responses to minimal amounts of epinephrine.

Hydrocortisone added without plas-

ma did not potentiate the response (Table 2).

Figure 2 demonstrates constant response to standard solution titration curves over the working day.

B. URINE PRESSOR ASSAYS WITH PLASMA AND HYDROCORTISONE POTENTIATED STRIP. 1. *In control subjects.* Three to 5-hour samples of morning urine from apparently health laboratory technicians obtained on several different days were assayed and the hourly output of pressor substance determined (Table 3). Repeat assays were performed on some of these urines on the second, fourth, and seventh day of storage. It is evident as indicated by others (Helmer[5]), that with acidification and refrigeration responses were stable for a period of at least 7 days. The results are comparable to those of Helmer[5] who found that the output of pressor material ranged from 1.6 to 6.6 gamma epinephrine equivalents per hour in 11 healthy laboratory workers.

Twenty-four hour collections of urine were obtained on 21 healthy adult controls. The 12 females in this group were found to have an average of 41.3 g.e.e. per 24 hours; the 9 males averaged 38.6 g.e.e. per 24 hours. The total group ranged from 15.8 to 68.9 g.e.e. per 24 hours. One additional male and female, not included in the above, showed values of "less than" 19 g.e.e. per 24 hours.

TABLE 2.—PERFORMANCE OF AORTIC STRIP WITHOUT AND WITH PLASMA OR HYDROCORTISONE, OR BOTH

	Krebs-Glucose Bath (ml.)	*Epinephrine (gamma)*	*Plasma (ml.)*	*Hydrocortisone (mg.)*	*Two-min. Rise (mm.)*	*Three-min. Rise (mm.)*
STRIP A	15	.04			12.5	12.5
	15	.02			2.0	2.0
	15	.04			10.0	10.0
	15	.02			1.5	1.0
	15	.04	0.2		16.5	17.5
	15	.02	0.2		4.0	4.5
	15	.04	0.2	0.2	22.5	25.5
	15	.02	0.2	0.2	11.0	13.5
	15	.04	0.2	0.2	24.5	28.5
	15	.02	0.2	0.2	11.5	14.0
	15	.04			14.0	16.0
	15	.02			3.5	2.5
	15	.04			2.0	1.5
	15	.02			0.0	0.0
	15	.02			0.0	0.0
	15	.04			1.0	0.0
STRIP B	15	.01			12.0	10.5
	15	.02			15.0	11.5
	15	.01			7.5	5.5
	15	.02			7.0	6.0
	15	.01		0.2	10.0	8.5
	15	.02		0.2	10.0	8.0
	15	.01		0.2	7.0	5.0
	15	.02		0.2	2.0	1.5
	15	.01	0.2	0.2	20.5	24.5
	15	.02	0.2	0.2	31.0	34.0
	15	.01	0.2	0.2	22.0	23.5
	15	.02	0.2	0.2	29.0	31.5

TABLE 3.—STABILITY OF STORED, REFRIGERATED, ACIDIFIED URINE
(Concentration: Gamma EPINEPHRINE EQUIV./L.)

Normal Control	*Sample*	*Subsequent tests on same urine*							*Gamma epinephrine equivalent Output/hour a.m. sample°*
		Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	
J.B.	a	42	40						1.5
	b	49	46					46	2.4
	c	18	17		19			20	.7
S.K.	a	100+	120						4.6
	b	36	48		49			43	1.3
	c	100+						82	
J.W.	a	64	86						2.6
	b	27	36		35			28	1.2
	a	89	97		96			112	2.5

Each horizontal line of results represents a different urine sample.

100+ —Just above 100
°Calculated from first result on each urine sample.

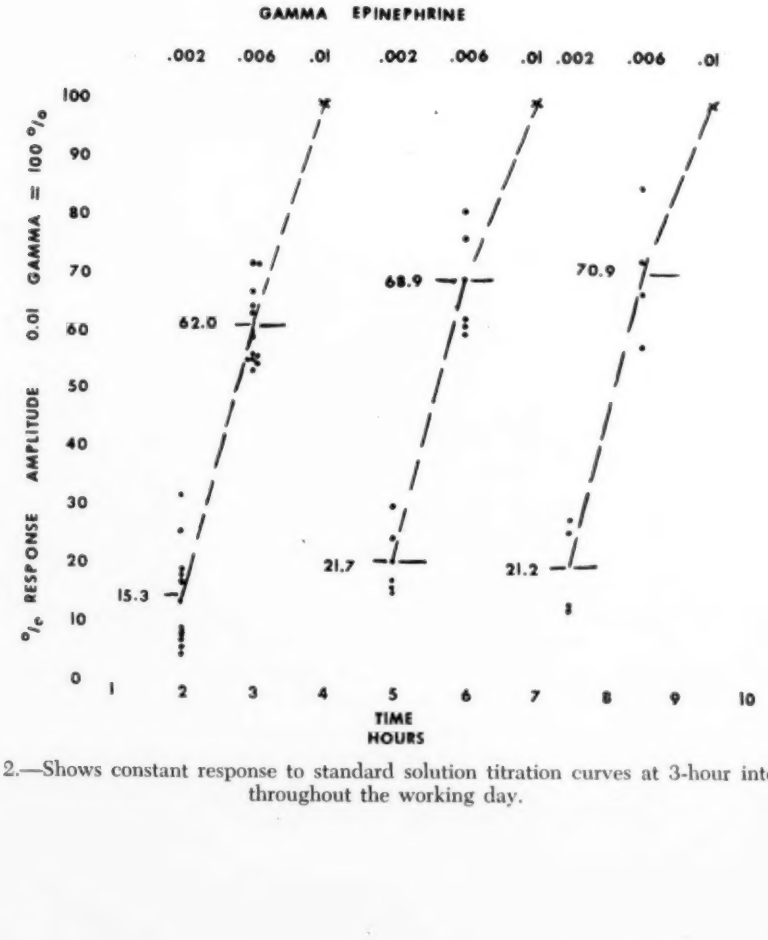


Fig. 2.—Shows constant response to standard solution titration curves at 3-hour intervals throughout the working day.

An additional series of 24-hour urinary pressor assays obtained from a group of apparently healthy male prisoners are shown in Fig. 3.

2. *In hospitalized patients not proved to have pheochromocytoma.* The medical records of 126 hospitalized patients, mostly hypertensive, whose urine had been submitted for routine pressor assay, were reviewed. An additional 33 patients on whom blood pressure data were available were included in the total analysis. Many of these urines were screened only for excessive amounts of pressor substance to rule out pheochromocytoma. Therefore in 58 of the patients the results were approximate and recorded as less than a certain equivalent amount of epinephrine per 24 hours. Of the 58, 15 patients had a 24-hour urine output of less than 10 g.e.e., 19 had less than 20 g.e.e., 18 less than 50, and 6 less than 120. Of the 68 precise values available 64 were based on 24-hour urine collections and 4 on 3- to 5-hour morning specimens. Four patients with pheochromocytoma are discussed later. In 60 patients the 24-hour excretion averaged 34.0 g.e.e. with a range of 4.6 to 155 g.e.e. In these there were no discernible differences in the 7 to 39 and 40 to 76 age groups, in whites or Negroes, or in groups divided on the basis of pulse rate. There was however a consistent sex difference. The 23 males ranged from 4.6 to 155 g.e.e. per 24 hours, with an average of 51.7 g.e.e. The 37 females ranged from 5.1 to 88 g.e.e. per 24 hours, with an average of

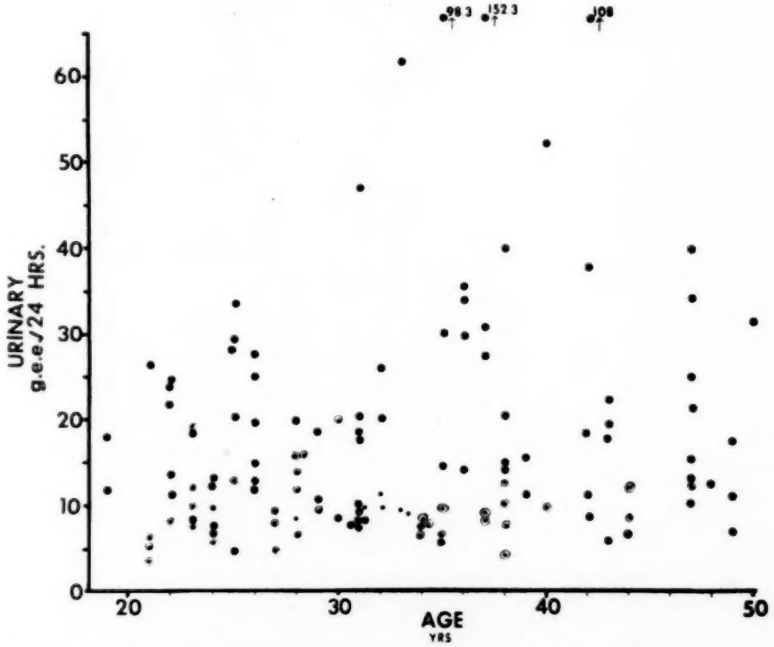


Fig. 3.—Scatter of 127 results obtained from 76 male prisoners (single repeat tests on 51) ranked according to age. Forty-six of the results were less than 20.4 g.e.e. per 24 hours (◉). The remaining 81 whole numbered results (•) ranged from 4.8 to 152.3 g.e.e. per 24 hours with a mean value of 24.0.

23.0 g.e.e. This sex difference was still present when the patients were divided with respect to age, blood pressure, or pulse rate.

There appeared to be an inverse relationship between the excretion of pressor substance and the blood pressure (Table 4). This has been variously reported by others (von Euler[1], Goldenberg and Rapport[3], Møller, Buus and Bierring[6]).

were greatly increased, that is, 800, 1072 and 9750 g.e.e. per 24 hours. A fourth patient with an output of 823 g.e.e. per 24 hours died following removal of the left adrenal and just prior to planned right adrenalectomy. There was no postmortem examination.

Discussion. The addition of plasma and of hydrocortisone to electrolyte-glucose solutions in which a strip of rabbit aorta is mounted accentuates

TABLE 4.

		Number	*Range (g.e.e. per 24 hrs.)*	*Mean (g.e.e. per 24 hrs.)*
A. Average Blood Pressure:				
1. Below 140/90	Males	5	(31.5– 95)	53.9
	Females	8	(5.1– 88)	31.0
	TOTAL	13		39.0
2. Between 140/90 and 190/120	Males	9	(21.8–113.4)	62.6
	Females	12	(8.2– 73.1)	24.6
	TOTAL	21		40.9
3. Above 190/120	Males	8	(4.6–155)	39.7
	Females	16	(5.1– 36.8)	12.0
	TOTAL	24		25.6
B. Blood Pressure on Test Day:				
1. Below 140/90	Males	4	(31.5–113.4)	69.4
	Females	6	(7.7– 88)	33.1
	TOTAL	10		47.6
2. Between 140/90 and 190/120	Males	12	(7.4–155)	48.6
	Females	16	(8.0– 78.5)	24.1
	TOTAL	28		31.0
3. Above 190/120	Males	2	(28.9– 44)	36.5
	Females	6	(10 – 20.8)	15.9
	TOTAL	8		21.1

The results from 33 consecutive additional patients were analyzed. The 15 additional males averaged 32 g.e.e. output per 24 hours and the 18 additional females averaged 25.1 g.e.e per 24 hours. The total group of 93 patients had an average output of 32.0 g.e.e. per 24 hours, with 38 males averaging 43.9 and 55 females averaging 23.7. This larger group showed a diminishing sex differential. As seen above, the small control group showed no sex differential.

3. *In patients with pheochromocytoma.* In 3 patients with proved pheochromocytoma the rates of excretion

the contraction and makes the responses more consistent. Our experience to date indicates that for routine rapid screening a reading lower than 100 to 120 g.e.e. per 24 hours is sufficient to rule out pheochromocytoma. Others have suggested a somewhat higher level, that is, 150 to 225 g.e.e. per 24 hours, but the assay methods have not been the same. In employing any of the available criteria it must be kept in mind of course that a pheochromocytoma may secrete at a low rate when quiescent.

Occasional false positive tests will occur. Thus the first assay of urine from

a 32-year-old female showed 502 g.e.e. per 24 hours. All other studies were negative including the regitine test, histamine test, cold pressor test, intravenous pyelography, and perirenal air study. Three subsequent assays on urine obtained when the blood pressure was similarly elevated revealed normal values of 18.2, 29.4 and 27.9 g.e.e. Also in this patient the pressor level in serum was normal, that is, less than 0.2 gamma per 100 ml. (von Euler[1], Pitkanen[7]). Repeated assays and the study of plasma argue against the presence of a pheochromocytoma in this patient, though this possibility has not as yet been excluded *in toto*. Hence, at least 2 assays should be run when there is any doubt. Similarly, a second determination is in order in an individual suspected of having a pheochromocytoma where the first sample was obtained during a period of normotension.

Summary. The sensitivity and reliability of a simple technique using a rabbit aorta strip for quantitative or semiquantitative determination of pressor substance in urine have been increased by the use of plasma and hydrocortisone. In 21 healthy adult controls the 24-hour excretion of pressor materials ranged from 15.8 to 61.9 g.e.e. per 24 hours with an average of 40.1 g.e.e. per 24 hours. Another series of 81 results from 76 males, aged 19 to 50, averaged 24.0 g.e.e. per 24 hours, with 46 additional results less than 20.4 g.e.e. per 24 hours. Ninety-three hospitalized patients without pheochromocytoma averaged 32.0 g.e.e. per 24 hours. An additional 58 patients had an output of less than 120 g.e.e. per 24 hours. In the hospitalized patients it was revealed that females had somewhat higher levels than males and that there was in the non-pheochromocytoma patients an inverse relationship between the amount of pressor substance in the urine and the blood pressure level. Four patients with pheochromocytoma had definitely elevated levels, above 800 g.e.e. per 24 hours.

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SUMMARIO IN INTERLINGUA

Le Potentiation e le Stabilisation del Effecto de Substantias Pressori, Observate in Bandas de Aorta Como Effecto de Plasma e de Hydrocortisona: Utilisation Routinari in le Diagnose de Pheochromocytoma

Le sensibilitate e le fidelitate de un simple technica, in que bandas de aorta de conilio es usate pro le determination quantitative o semiquantitative de substantia pressori in specimens de urina, esseva augmentate per le uso de plasma e de hydrocortisona. In 21 normal adulte subjectos de controlo, le excretion de materiales pressori in le urina de 24 horas variava inter 15,8 e 61,9 e.g.e. (= equivalente de gamma de epinephrina). Le valor medie esseva 40,1 e.g.e. per

24 horas. In un altere serie de 127 resultatos ab 76 masculos de etates de inter 19 e 50 annos, 46 esseva inspecificatemente infra 20,4 e.g.e. per 24 horas durante que le remanente 81 resultatos specificamente determinate amontava a un valor medie de 24,0 e.g.e. per 24 horas. In un serie de 151 patientes hospitalisate, 58 monstrava valores inspecificatemente infra 120 e.g.e. per 24 horas, durante que le remanente resultatos specificamente determinate amontava a un valor medie de 32,0 e.g.e. per 24 horas. Nulle de iste patientes habeva pheochromocytoma. Esseva notate un relation inverse inter le quantitate de substantia pressori in le urina e le nivello del tension de sanguine. Esseva etiam notate in iste serie de patientes sin pheochromocytoma que le activitate de substantia pressori in le urina esseva levemente plus alte in le caso de masculos que in le caso de femininas. Esseva studiate quatro patientes con pheochromocytoma. In illes omnes le nivello de activitate pressori in le urina esseva definitemente elevate, *i.e.* sin exception supra 800 e.g.e. per 24 horas.

SUMMARIO IN INTERLINGUA

(See page 154 for original article)

Administration Intravenose de Mecamylamina (Inversina) Como Medio pro Determinar le Efficace Dosage Oral

1. Le reduction del tension de sanguine constatate post le administration intravenose de mecamylamina es ben correlationate con le dosage oral que es requirite pro producer un satisfacente responsa antihypertensive.
2. Durante un periodo de inter 1 e 3 dies immediatemente post le administration intravenose del droga, un sol dose oral de mecamylamina per die non debe esser excedite. Post iste periodo il es usualmente necessari administrar le indicate dose omne 12 horas.
3. Le tension sanguinee orthostatic deberea esser usate como guida in terminar le infusion intravenose de mecamylamina, proque alteremente sever e prolongate formas de hypotension pote resultar.

(Continued from page 193)

sanguine que es rendite possibile per le vehiculo empleate. In le lumine de iste constatationes, le classification de theophyllina super le base de experimentos animal como un "maligne vasodilatator coronari" debe esser rejicite pro le patiente human.

Derivatos de xanthina, in administrationes tanto per via intravenose como etiam per via oral, deberea esser rehabilitate como agentes de tractamento pro angina de pectore e altere statos de morbo coronari. Al tempore presente, le plus efficace preparato pro le administration oral es un solution hydro-alcoholic de theophyllina, sed altere derivatos e preparatos de compositos del gruppo xanthinic deberea esser explorate meticulosemente pro render possibile un plus extense uso de illos in le tractamento de coronari morbo cardiac.

URINARY SODIUM RETENTION AFTER ACTH STIMULATION: A RAPID, SIMPLE SCREENING TEST FOR ADRENAL CORTICAL INSUFFICIENCY

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and

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There is need for a rapid, simple, safe, and economical screening test for adrenal cortical reserve function.

Previous tests have proved to be either cumbersome, unreliable, technically difficult, or of questionable diagnostic value, particularly in borderline cases. The ACTH-Eosinophil Test (Thorn *et al.*[14]) has been used most widely but has been unsatisfactory in general hospitals because of the unreliability of eosinophil counting. The urinary ketosteroid response to ACTH administration (DeFilippis and Young[4]) is costly and requires 48 to 72 hours and reliable collections of 24-hour urine samples. The Kepler-Power-Robinson Water Test[6] requires a 3-day preparation period and determinations of plasma and urinary concentrations of urea and chlorides.

The Cutler-Power-Wilder Test[3] is too dangerous for general use. During the Insulin Intolerance Test (Fraser, Albright and Smith[5]) severe, to fatal hypoglycemia may develop. Perlmutter[9] has proposed a test which compares the sodium concentration in the plasma and urine of patients showing clinical evidence of shock and hyponatremia. However, hyponatremia and shock are variable manifestations of early adrenal cortical insufficiency.

The authors herein propose a 4-hour screening test which requires no elaborate collecting or testing. It is based on the well-known observation of urinary sodium retention following the administration of ACTH to a subject with a responsive adrenal cortex.

Methods and Materials. The procedure for the test was as follows: 1) The patient was awakened at 6:00 A.M. and given 400 ml. of water to drink. No food was given throughout the period of the testing. 2) The patient was asked to void at 7:00 A.M. (discard) and 25 units of aqueous ACTH given intramuscularly. Another 400 ml. of water was ingested within a 5-minute period. 3) The patient voided at 8:00 A.M. and the urine specimen was saved and labeled SAMPLE NO. 1. Another 200 ml. of water was ingested. Whenever there was difficulty in voiding spontaneously, the patient was catheterized. 4) At 9:00 A.M., the patient ingested 200 ml. of water. 5) At 10:00 A.M., the patient voided and the specimen was discarded. Another 200 ml. of water was ingested. 6) At 11:00 A.M., the patient voided again, and this specimen was preserved and labeled SAMPLE NO. 2.

The water was given at hourly intervals to assure a fairly constant urinary output in amounts to allow for spontaneous micturition.

The sodium, potassium, and chloride content, Na to K ratio, specific gravity, pH, and volume were determined on the urinary specimens. The data were charted for comparison.

Determinations of pH were made by means of a Beckman Model H-2 line-operated pH meter.

Chloride determinations were made by means of titrations with standard mercuric nitrate solution using s-diphenyl carbazone as an indicator (Reiner[11]). Estimations of sodium and potassium concentrations were made by the method of Mosher *et al.*[8] using a

Beckman spectrophotometer model DU with a Beckman Model 10300 flame photometer attachment which utilizes air, oxygen and natural gas.

Results. A. NORMAL SUBJECTS. Control experiments were conducted the morning prior to the testing in order to ascertain the normal excretory pattern of urinary electrolytes in the fasting subjects in response to the ingestion of additional 200 ml. every hour until 11:00 A.M. A rather constant urinary output was obtained for each hour of testing. Catheterization was rarely necessary in the control subject.

On the following morning, the test was repeated in the same manner, with the exception that the subject was given 25 units of aqueous ACTH intramuscularly at 7:00 A.M. See Tables 3 and 4.

TABLE 1.—URINE EXCRETION TEST
Patient: J.A. No ACTH.

Sample Time	*Vol. ml.*	*Sp. Gr.*	*pH*	*mEq./liter*			
				Na	*K*	*Cl*	*Na/K*
6:00 A.M.	380	1.022	6.33	123	42.5	107	2.89
7:00	370	1.007	6.12	46.3	21.6	52.6	2.14
8:00	395	1.004	6.40	41.9	17.0	46.1	2.46
9:00	220	1.012	6.01	48.8	26.3	64.1	1.86
10:00	235	1.012	6.52	51.4	22.9	58.9	2.24
11:00	220	1.003	6.60	51.7	23.2	60.5	2.22
Noon	205	1.005	6.39	50.2	17.6	57.3	2.85

TABLE 2.—URINE EXCRETION TEST
Patient: L.K. No ACTH.

Sample Time	*Vol. ml.*	*Sp. Gr.*	*pH*	*mEq./liter*			
				Na	*K*	*Cl*	*Na/K*
6:00 A.M.	180	1.014	6.52	54.0	42.1	53.2	1.28
7:00	141	1.009	6.76	48.9	23.3	44.2	2.09
8:00	183	1.005	6.90	22.0	7.02	16.3	3.13
9:00	191	1.007	7.18	24.6	9.37	26.5	2.84
10:00	184	1.006	7.04	32.2	8.08	22.0	3.99
11:00	187	1.005	7.07	32.2	9.23	25.9	2.49
Noon	165	1.004	7.05	34.2	8.78	27.3	3.90

water. Urine specimens were collected at hourly intervals and the pertinent determinations were made. It soon became apparent that no significant changes occurred in the urinary concentrations of sodium, potassium, and chloride, or Na to K ratio during the period of testing (See Tables 1 and 2).

Initially, we had the subject void at 6:00 A.M. after ingesting 400 ml. of water. Thereafter, hourly urine specimens were collected until 12 noon. The subject ingested another 400 ml. of water at 7:00 A.M. and an

It became apparent that the maximal fall in urinary sodium concentration occurred 4 hours after the injection of ACTH. The nocturnal concentration of urinary sodium was generally higher than the specimen taken at 7:00 A.M., one hour after the ingestion of 400 ml. of water.

The authors concluded that comparison of the urinary concentrations of sodium in the 8:00 and 11:00 A.M. specimens offered the optimal urinary electrolyte response to the administration of ACTH. Thereafter the testing

TABLE 3.—URINE EXCRETION TEST
Patient: J.A. 25 units aq. ACTH, i.m. at 7:00 A.M.

Sample Time	Vol. ml.	Sp. Gr.	pH	mEq./liter Na	K	Cl	Na/K
6:00 A.M.	460	1.018	6.25	126	43.0	97.9	2.93
7:00	220	1.006	6.27	57.5	21.8	54.5	2.64
8:00	225	1.005	6.73	52.3	22.9	54.2	2.28
9:00	100	1.008	6.72	69.6	59.5	97.0	1.17
10:00	205	1.005	6.65	29.0	34.5	42.4	0.84
11:00	290	1.003	6.83	23.0	22.4	26.0	1.03
Noon	310	1.003	6.88	23.0	22.7	25.0	1.01

TABLE 4.—URINE EXCRETION TEST
Patient: L.K. 25 units aq. ACTH, i.m. at 7:00 A.M.

Sample Time	Vol. ml.	Sp. Gr.	pH	mEq./liter Na	K	Cl	Na/K
6:00 A.M.	174	1.007	6.91	39.2	20.6	34.4	1.90
7:00	188	1.012	6.85	28.1	24.6	25.5	1.14
8:00	178	1.007	7.11	41.4	10.0	35.9	4.14
9:00	180	1.009	7.20	32.5	9.55	30.3	3.41
10:00	185	1.004	7.12	22.1	8.48	18.5	2.61
11:00	164	1.009	7.21	16.5	8.47	13.2	1.95
Noon	181	1.008	7.15	16.3	8.61	12.8	1.89

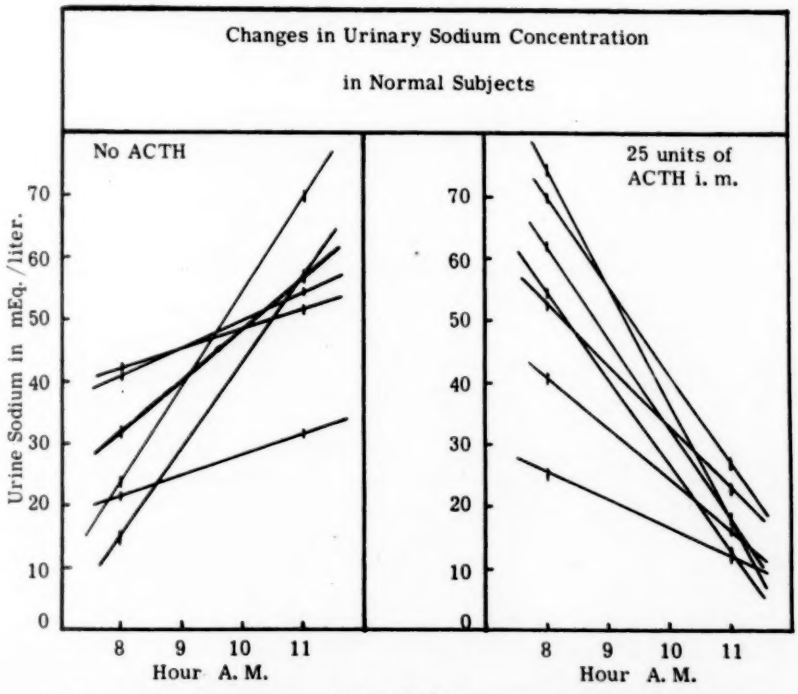

Fig. 1.—Response of normal individuals to urinary sodium-ACTH test.

was simplified to include only these two specimens.

A summary of the responses obtained to ACTH stimulation in subjects who apparently had normal adrenal cortices is presented in Fig. 1. A reduction in the urinary sodium concentration in excess of 50% occurred in all cases.

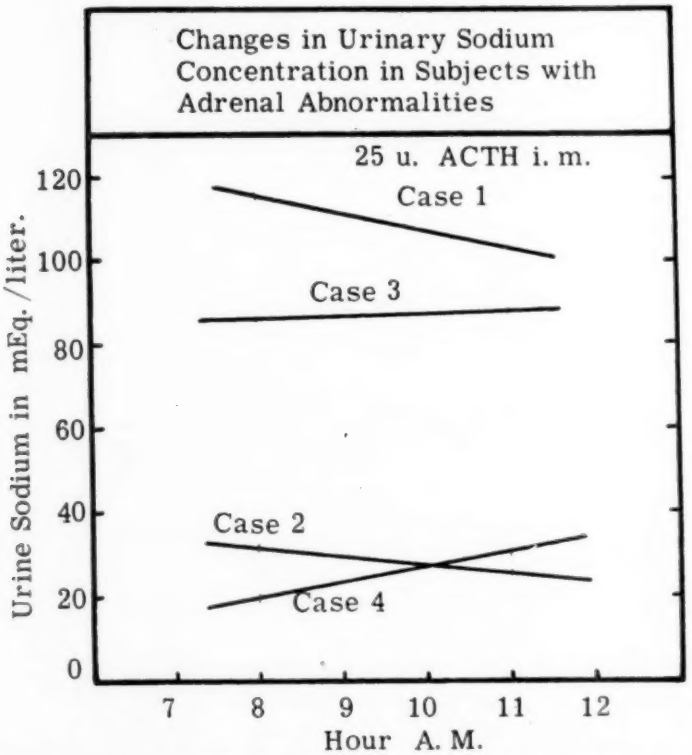

Fig. 2.—Response of individuals with known adrenal abnormalities to urinary sodium-ACTH test.

B. PATIENTS WITH ABNORMALITIES OF ADRENAL CORTICES. A summary of the responses to ACTH administration of patients with known unresponsive adrenal cortices is presented in Fig. 2.

Case 1. G.B., a 45-year-old Negro housewife with classical Addison's disease of 10 years' duration was given 25 units of ACTH. No significant change in the urinary sodium concentration was observed in response to ACTH administration during the 4-hour test period.

Case 2. J.E., a 60-year-old Negro factory worker, suffering from advanced rheumatoid arthritis, had been maintained on 30 mg. of prednisolone daily. Administration of 25 units of ACTH failed to cause a significant change in urinary sodium concentration.

Case 3. E.C., a 45-year-old Negro housewife was suffering from dermatomyositis. She had been maintained on 30 mg. of prednisolone daily. She showed evidence of hyperadrenocorticism characterized by the so-called "moon-face" and mild hypertension. No

change in urinary sodium concentration was noted after administration of ACTH. Apparently the adrenal cortex was unresponsive due to exogenous corticosteroid therapy.

Case 4. S.R., a 42-year-old white housewife was suffering from hyperplasia of the adrenal cortex (Cushing syndrome). Her 17-hydroxysteroid output was 38.3 mg. per 24 hours. She was given 8 mg. of 9 alpha-fluorohydrocortisone and the 17-hydroxysteroid output fell to 9 mg. per 24 hours. This indicated depression of the hyperplastic adrenal cortex to exogenous corticosteroid administration. However, administration of adrenocorticotrophin apparently failed to stimulate the hyperplastic adrenal cortices, thus giving a urinary excretion test which resembled that observed in patients with Addison's disease and hypoadrenocorticism secondary to exogenous administration of corticosteroid.

Discussion. Numerous investigators (Prunty[10], Thorn[13], Thorn, Laidlaw and Goldfein[15], Wahi, Ramachandran and Navani[17]) have substantiated the concept that patients suffering from adrenal cortical insufficiency, whether induced or spontaneous, fail to show a specific response to ACTH stimulation. There is no significant fall in the circulating eosinophils or increase in the urinary uric acid to creatinine ratio. The 24-hour urinary 17-ketosteroid excretion remains unchanged (De Filippis and Young[4]). Likewise, the authors failed to observe any significant change in the concentration of urinary sodium in patients with depressed adrenal cortical responsiveness.

Measurement of the specific response of urinary sodium retention to ACTH stimulation does not necessarily reflect the overall integrity of the complex functions of the adrenal cortex, but it does indicate the mineralo-corticoid activity (Thorn[13]). However, as is well-known, when a patient with adrenal cortical insufficiency encounters difficulty in handling electrolytes (mineralo-corticoid deficiency), serious clinical problems arise.

The adrenal cortex secretes several hormones which play variable roles in the renal tubular reabsorption of sodium (Liddle[7]). Aldosterone is the most potent "salt-retaining" hormone known (Tait, Simpson and Grundy[12]). However, other mineralo-corticoids probably play a significant role in the normal tubular reabsorption of electrolytes (Thorn, Laidlaw and Goldfein[15]).

In general, the eosinophil-response test may be used as a measure of secretion of 11-17 oxysteroids by the adrenal cortex (Thorn[13]). The fall in circulating eosinophils is observed within 4 hours. This observation may be correlated with a rise in blood levels of 11-17 oxycorticoids which occurs within the same time interval (Christy, Wallace and Jailer[2], Winton[18]). Since the change noted in the urinary excretion of sodium likewise takes place within 4 hours, the authors postulate that the sodium retention observed after the intramuscular injection of 25 units of ACTH is probably mediated through increased secretion of 11-17 oxycorticosteroid by the intact, responsive adrenal cortex. It is unlikely that the marked fall in the concentration of urinary sodium is mediated through increased secretion of aldosterone, since other investigators (Axelrad, Johnson and Luetcher[1], Venning *et al.*[16]) have shown no significant rise in this hormone following the injection of ACTH.

Summary. 1. A rapid, simple screening test for the detection of adrenal cortical insufficiency has been presented.

2. Greater than 50% reduction in urinary sodium concentration was observed 4 hours after the intramuscular administration of 25 units of ACTH in

subjects with responsive adrenal cortices.

3. No significant fall in urinary sodium concentration was observed after ACTH administration in patients with known hypoadrenocorticism during the 4-hour test period.

4. Further studies are contemplated to evaluate the usefulness of the urinary sodium-ACTH test.

ACKNOWLEDGMENTS: We wish to express appreciation to Dr. Norman E. Clarke, Sr., for his encouragement and helpful suggestions and to Drs. Thomas Billingslea and Adam Kossayda for the opportunity to study patients G.B. and S.R., respectively.

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SUMMARIO IN INTERLINGUA

Retention de Natrium Urinari post Stimulation a ACTH: Un Simple e Rapide Test de Elimination pro Insufficientia del Cortice Suprarenal

1. Un rapide e simple test de elimination pro le detection de insufficientia del cortice suprarenal es presentate.

2. Reductiones de plus que 50 pro cento in le concentration urinari de natrium esseva observate 4 horas post le administration intramuscular de 25 unitates de ACTH in subjectos con respondente cortices suprarenal.

3. Nulle significative reduction del concentration de natrium esseva observate in le curso del periodo experimental de 4 horas post le administration de ACTH in patientes con cognoscite hypoadrenocorticismo.

4. Studios additional es planate pro evalutar le utilitate del test de natrium urinari post ACTH.

QUINIDINE IN CHRONIC ATRIAL FIBRILLATION

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Attempts at reversion of chronic atrial fibrillation to normal sinus rhythm have been recorded over the years with varying indications, results, untoward reactions and degrees of enthusiasm.

In 1929 Wolff and White[8] reported a series of 62 cases of atrial fibrillation in which 65.7% were restored to normal rhythm by the use of quinidine. Digitalization was considered to be desirable and no untoward effects were noted. More recently Gold's[1] report of experiments conducted on dogs indicated that the concomitant use of digitalis and quinidine resulted in an increased number of arrhythmias. In 1935 Kohn and Levine[5] questioned "whether any form of therapy to restore normal rhythm is warranted." They felt that mere reversion was no criterion of the value of the drug and popularized the idea that the "sudden onset of normal rhythm is an important factor in the production of emboli."

In 1947 McMillan and Welfare[6] reported a series of 50 cases in which 44 were reverted. As justification for the attempts at reversion they noted that experimentally induced atrial fibrillation reduced cardiac output by as much as 40% and that the cardiorespiratory mechanism was improved by the restoration of normal rhythm. Hecht, Osher and Samuels[3] in 1951 studied the respiratory and cardiac functions of patients with organic heart disease before and after reversion, both at rest and after exercise. They noted that cardiac output improved and that oxygen extraction rose after reversion. Pulmonary ventilation after exercise rose only slightly in the reverted group as compared to a striking rise in the fibrillating group. The arteriovenous oxygen difference was significantly higher in the fibrillating group than in the reverted group. It was felt, therefore, that cardiac reserve was definitely improved by reversion.

In rebuttal to the argument that effective *auricular* contractions would tend to loosen mural thrombi, McMillan and Welfare offered electrocardiographic and direct visual evidence that fairly frequent, apparently normal *auricular* contractions occurred in the course of atrial fibrillation. Fifty-four per cent of their patients had mild toxic reactions to quinidine, consisting of nausea, anorexia, headache, drowsiness and tinnitus and 10% had severe reactions consisting of syncope, pulmonary embolism, peripheral collapse

and delirium. In 4 patients, rhythm reverted to normal 3 to 8 hours after cessation of therapy.

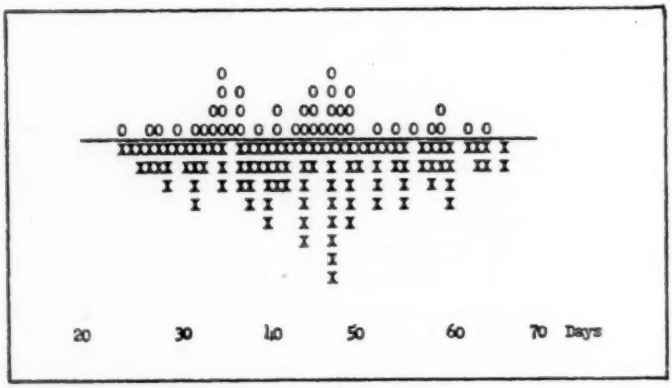
In 1950 Goldman[2] reported a series of 48 cases in which close electrocardiographic observation revealed the occurrence of atrial flutter in 34 during the attempted reversion period. Sinus rhythm was restored by quinidine therapy in 26 of the 34 patients. In another series of 155 patients in which 76% were reverted, Yount, Rosenblum and McMillan[9] noted that 8 passed through atrial flutter.

Holzman and Brown[4] in 1951 reported a series of 57 attempts in which 53% were reverted. They observed that the atrial rate was slowed by quinidine regardless of the cardiac mechanism and that reversion reduced the size of the dilated *auricle*, thereby reducing the incidence of embolization.

More recently Sokolow and Ball[7] successfully reverted 74% of 177 patients. It was their feeling that the use of quinidine should be considered as a calculated risk and that "knowledge of the serum quinidine concentrations should decrease the risk by indicating the statistical likelihood of toxicity at increasing concentrations of the drug."

Since the consensus of these reports indicated both a theoretical and clinical advantage of normal sinus rhythm over atrial fibrillation, it was felt that attempts to restore normal sinus rhythm were worthwhile, provided precautions were taken against the toxic effects of quinidine.

Material and Method. The records of 100 unselected, consecutive hospitalized patients, admitted between 1946 and 1952, with heart disease and atrial fibrillation of at least 2 weeks' duration, were reviewed. All had a history of cardiac decompensation or were decompensated upon admission and had evidences of valvular or myocardial disease, as shown by abnormal physical signs, roentgenograms or electrocardiograms, and were treated by bed rest, salt restriction, digitalization and mercurial diuretics when necessary. Another series of 100 unselected patients, admitted between 1953 and 1958, were treated in the same manner with the addition of anticoagulants and quinidine. Dicumarol was so administered that the prothrombin times ranged in the neighborhood of twice that of controls for a period of 12 to 14 days prior to the administration of quinidine. This was done in deference to those who agreed with Kohn and Levine that restoration to



x = Control (period of hospitalization)
0 = Treated but unreverted (period of hospitalization)

Fig. 1.—Observed number of days of fibrillation.

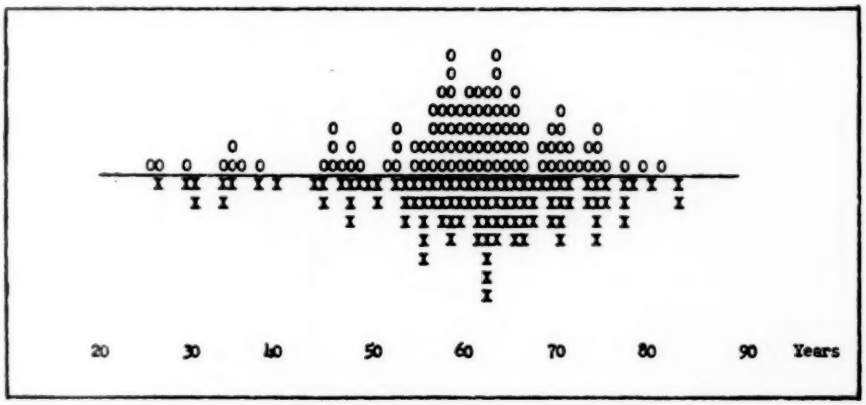
normal sinus rhythm increased embolization and on the assumption that a 2-week period of anticoagulant therapy would prevent new thrombus formation and permit existing thrombi to organize. Quinidine sulfate was then administered in doses of 0.2 gm. every 2 hours for 6 doses. An electrocardiogram was taken between the fourth and fifth doses. If the QRS duration was not increased by 25% or more, the remaining two doses of the series were administered. If severe nausea, vomiting, diarrhea, tinnitus or prolongation of the QRS complex beyond 25% of the control occurred, the drug was discontinued. If no untoward effects were noted the schedule was repeated on the following days with an increment of 0.2 gm. of quinidine sulfate per dose per day until reversion was effected, toxic effects were evident, or a dose of 1 gm. every 2 hours was reached. A maintenance dose of 0.2 gm. to 0.4 gm. of quinidine sulfate was given every 6 hours if reversion was accomplished. Dicumarol therapy was maintained for an additional 3 days following reversion.

The average known duration of fibrillation in the control group, which corresponded to the period of hospitalization, was 44.8 days, while that of the treated group which did not revert was 43.2 days. The shortest of the control group was 24 days and the longest, 64 days. The shortest of the treated group which did not revert was 24 days and the longest, 66 days. The distributions are demonstrated in the following diagram.

The average age of the patients in the control group was 58.7 years, while that of those in the treated group was 59.5 years. The youngest of the control group was 27 years and the oldest, 84. The youngest of the treated group was 26 years and the oldest, 82. The following diagram demonstrates the respective age distribution.

Of the control group, 82 had arteriosclerotic heart disease, 11 had rheumatic heart disease and 7, combinations of arteriosclerotic and hypertensive cardiovascular disease. Of the treated group 79 had arteriosclerotic heart disease, 11 rheumatic heart disease and 10, combinations of arteriosclerotic and hypertensive cardiovascular disease.

From the foregoing, it is evident that the control and treated groups were comparable insofar as observed duration of fibrillation, ages of patients and types of heart disease. It would appear reasonable to presume that those of the treated group who reverted would have continued to fibrillate for a period of time corresponding to their respective durations of hospitalization, had not antifibrillating measures been undertaken.



x = Control
0 = Treated

Fig. 2.—Age distribution.

Results. Table 1 summarizes our observations.

Only one of the control group spontaneously reverted under the regimen outlined, whereas 57 of the treated group reverted. There were 18 deaths among the control group compared to one in the treated group. Seven of the 11 necropsied cases among the 18 dead

in the control group exhibited thromboembolic phenomena which accounted for the deaths of these patients. There was clinical evidence of possible cerebral or pulmonary infarction in 3 of the remaining 7 who were not necropsied and in 4 of the 82 who survived, whereas there were no recognizable thromboembolic complications in the treated group.

TABLE 1

	No.	*No. Reverted*	*Average No. Days of Maintenance of Reversion*	*Mortality*	*Necropsy Findings*	*Not Necropsied*
CONTROL						
Rheumatic Heart Disease	11	0	0	3	1-pulmonary edema with renal infarction 1-myocardial infarction and renal infarction	1
Arteriosclerotic Heart Disease	82	1	43	14	1-pulmonary infarct 4-cerebral infarction 4-extensive coronary sclerosis	5
Combined Arteriosclerotic Heart Disease and Hypertensive Cardiovascular Disease	7	0	0	1	—	1
TOTAL	100	1	43	18		7
TREATED						
Rheumatic Heart Disease	11	2	14	0	—	0
Arteriosclerotic Heart Disease	79	47	25	1	—	1
Combined Arteriosclerotic Heart Disease and Hypertensive Cardiovascular Disease	10	8	26	0	—	0
TOTAL	100	57	24.7	1		1

Maintenance of normal sinus rhythm was effected by a quinidine dosage of 0.2 gm. every 6 hours in 27 cases, 0.4 gm. every 6 hours in 23, and 0.6 gm. every 6 hours in 3.

Of the complications responsible for cessation of therapy, 18 patients exhibited severe nausea; 7, diarrhea; 6, significant widening of the QRS complex; 3, severe dizziness; 2, multiple premature contractions; 2, severe tinnitus; 2, severe chest pain; and one, ventricular tachycardia. Two received maximal doses of 1 gm. of quinidine sulfate every 2 hours for 6 doses without untoward effect or reversion and the therapy was abandoned. Atrial flutter with 2:1 or 4:1 block occurred in 5 instances, 3 times during successful reversion and twice without reversion. In each of the latter two, fibrillation reappeared following quinidine withdrawal.

Of 5 patients with bundle branch block (1 with right and 4 with left) 3 reverted to normal sinus rhythm (1 with right and 2 with left). The 3 patients with the largest hearts, demonstrated roentgenologically, were successfully reverted without untoward incident.

Ten of this group who exhibited evidences of decompensation at the time of attempted reversion, despite adequate digitalization, bed rest, low salt diet and mercurial diuretics for at least

14 days, fully compensated after reversion to normal sinus rhythm. Seven others of this group, resistant to attempts at reversion remained somewhat decompensated at the termination of their respective periods of hospitalization.

The single death in the treated group occurred in an individual who was persistently decompensated until the time of his death 37 days after admission. His rhythm failed to revert after quinidine sulfate was pushed to 0.6 gm. × 4, when he developed nausea, vomiting and diarrhea which precluded further administration of the drug. The drug was discontinued 20 days prior to his death. Intractable failure rather than thromboembolic phenomena apparently accounted for his demise.

Discussion. It is apparent that the single death and absence of thromboembolic complications in the anticoagulated and quinidinized group are in marked contrast to the 18 deaths and 4% additional probable embolic complications in the control group. It is entirely possible that the failure to compensate in 19 of the control group resulted from persistence of the atrial fibrillation, since none of the 57 who reverted exhibited persistent decompensation. The absence of thromboembolic phenomena in the quinidine treated group was most likely due to the prophylactic anticoagulant therapy. Even those 43 who did not revert exhibited no evidence of emboli. Of the 100 who received no anticoagulants or quinidine, 7 exhibited necropsy and 4, clinical evidence of embolization. Bundle branch block and extreme cardiomegaly offered no particular obstacles to successful reversion, nor were unusual complications encountered. On the basis of the 10 patients who were more completely compensated after reversion, as compared to the 19 who were persistently decompensated while unreverted, it would appear that the restoration of normal rhythm effected more adequate compensation.

Summary and Conclusions. 1. One hundred patients hospitalized with chronic atrial fibrillation were subjected to Dicumarol anticoagulation and quinidine administration to the point of reversion, toxicity or 1 gm. every 2 hours for 6 doses.

2. Prolongation of the prothrombin time to twice that of controls was effected by Dicumarol administration over a period of 12 to 14 days prior to attempted reversion.

3. Fifty-seven reverted to normal sinus rhythm and were so maintained on smaller doses of quinidine throughout the remainder of their respective periods of hospitalization.

4. There was one death secondary to resistant decompensation and no embolic complications in the anticoagulated and quinidinized group, compared to 18 deaths and a 4% incidence of non-fatal thromboembolic complications in the untreated group.

5. Ten patients who were still decompensated at the time of the attempted reversion, in spite of intensive therapy for 14 days, fully compensated upon reversion and maintenance of normal sinus rhythm.

6. Patients with bundle branch block and marked cardiomegaly fared no worse than others.

7. On the basis of these observations, it would appear safe and desirable to use vigorous measures directed toward establishing normal sinus rhythm on all hospitalized patients with chronic atrial fibrillation.

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SUMMARIO IN INTERLINGUA

Quinidina in Chronic Fibrillation Atrial

1. Cento patientes, hospitalisate pro chronic fibrillation atrial, esseva subjicite a anticoagulation per Dicumarol e administrationes de quinidina usque a reversion, toxicitate, o 1 g per 2 horas pro 6 doses.

2. Prolongation del tempore de prothrombina a duo vices le valores de controlo esseva effectuate per le administration de Dicumarol durante un periodo de 12 a 14 dies ante le tentativa de initiar le reversion.

3. Cinquanta-septe patientes reverteva a normal rhythmos sinusal, e isto esseva mantenite con reducite doses de quinidina usque al fin del periodo de hospitalisation.

4. Occurreva un morte secundari a discompensation resistente e nulle complicationes embolic in le gruppo tractate con anticoagulante e quinidina, comparate con 18 mortes e un incidentia de 4% de non-mortal complicationes thromboembolic in le gruppo non assi tractate.

5. Dece patientes, qui al tempore del tentativa de effectuar reversion esseva ancora discompensate in despecto de un intense therapia de 14 dies de duration, attingeva un compensation complete post le reversion e manteneva normalitate de rhythmo sinusal.

6. Patientes con bloco de branca e marcate grados de cardiomegalia non respondeva minus favorabilemente que le alteres.

7. Super le base de iste observationes il pare justificate recommendar le uso de vigorose mesuras visante a establir un normal rhythmo sinusal in omne patientes hospitalisate con chronic fibrillation atrial.

ARE THE XANTHINES EFFECTIVE IN ANGINA PECTORIS?

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Xanthines have been used in the treatment of angina pectoris since 1895 when Askanazy[2] reported improvement in this disorder from the administration of theobromine sodium salicylate. Although slowly adopted at first, this series of drugs attained wide popularity in succeeding decades following the repeated demonstration of their direct vasodilator action on the coronary arteries of experimental animals. In 1925, however, Smith, Miller and Graber[32] found that while caffein sodio-benzoate and theobromine sodio-salicylate had little effect on the rate of perfusion of the coronary arteries of the rabbit, theophylline produced an increase in coronary flow of from 20 to 45%, and theophylline ethylenediamine (aminophylline) augmented coronary flow from 40 to 90%. Chiefly on the basis of these observations, aminophylline has largely displaced theobromine and other xanthine derivatives and in some quarters has become firmly entrenched as a "valuable" therapeutic agent in the treatment of coronary artery disease. Nevertheless, because of various conflicting clinical and experimental findings, physicians, to the present day, are divided regarding the benefits which can be derived from any of these agents in the treatment of ischemic heart disorders.

Supporting the possible usefulness of these drugs are the observations that aminophylline promotes the development of the collateral circulation to a myocardial infarct (Fowler, Hurevitz and Smith[8]) and lowers the mortality rate in experimental coronary occlusion (LeRoy, Fenn and Gilbert[13]). On a clinical level, Barnum and associates[3] have reported a lower mortality rate and incidence of thromboembolic complications in patients with acute myocardial infarction receiving xanthines than in those treated by other conventional regimens. Similarly, clinical observations by numerous investigators indicate that, in arteriosclerotic heart disease, xanthine derivatives may not only ameliorate anginal pain but also improve the efficiency of the heart. Even more convincing is the observation of Levy, Bruenn and Williams[14] that, in patients made anoxemic by the inhalation of oxygen-deficient mixtures, aminophylline delays the onset of anginal pain.

In direct contradiction to these findings are the careful studies of Schmidt[31] in dogs. Thus, the quantitative measurements of this investigator appear to indicate that the increase in coronary flow attending the administration of aminophylline is merely a partial and unsuccessful attempt to compensate for increased myocardial anoxia resulting from increased cardiac work and decreased myocardial efficiency. Consequently, Schmidt has characterized aminophylline as an "undesirable or malignant coronary vasodilator." Consistent with this concept is the finding that the administration of aminophylline by mouth was not associated with improvement in exercise tolerance in carefully designated studies of patients with angina pectoris. Indeed, poor therapeutic effects from oral administration have been reported by Evans and Hoyle[7], Wayne and Laplace[34], Gold, Kwit and Otto[10], Master, Jaffe and

Dack[15], and others. Such observations by independent investigators led to the inescapable conclusion that in large groups of patients aminophylline orally has no more effect on anginal pain than a placebo. However, while the value of this medicament by the oral route remains controversial, we have recently obtained unequivocal objective evidence of the efficacy of aminophylline when administered parenterally. Thus, in our laboratory the intravenous administration of 500 mg. of this drug was found to exert a marked modifying influence on the electrocardiographic response to standard exercise (Master two-step test) in a large segment of the patients studied. In sharp contrast, oral administration in usual recommended dosage (100 to 200 mg. t.i.d.) proved ineffective in all patients tested by this means as did a single large dose of 400 mg. of the drug. Consequently, it seems reasonable to assume that the failure with oral therapy may be ascribed to the inadequate blood theophylline levels attained as a consequence of inadequate dosage, poor absorption from the gastrointestinal tract, or both. Moreover, inasmuch as gastrointestinal intolerance precludes an increase in the dosage of this agent above 200 mg., a need exists for other theophylline derivatives or preparations in which greater solubility and lesser toxicity may permit higher dosage, better absorption, and more effective blood levels. Recently choline theophyllinate has been enthusiastically endorsed as a xanthine possessing all of these attributes (Aravanis and Luisada[1], Batterman *et al.*[4], Duesel and Fand[6], Gagliani, DeGraff and Kupperman[9]). Thus, theophylline blood levels have been shown to be 60 to 75% higher for the first 2 hours and 40 to 50% higher for the third and fourth hours with choline theophyllinate as compared with aminophylline (Gagliani, DeGraff and Kupperman[9]). Although Batterman and associates[4] and Aravanis and Luisada[1] have reported the drug to be effective in the treatment of patients with angina pectoris, our own observations with doses of 200 mg. 3 or 4 times daily, as recommended, have failed to detect significant improvement in exercise-electrocardiographic tests. While benefit was observed in such tests with twice the recommended dosage, that is, 400 mg. t.i.d., gastrointestinal distress did not permit the continuation of therapy at this dosage level.

More recently a preparation of theophylline in the form of a specially prepared elixir (Elixophyllin) has been shown to be associated with rapid absorption and attainment of high blood concentrations (Schluger, McGinn and Hennessy[30]). Thus, mean theophylline blood levels 15 minutes following administration were found to be 8 times higher with this preparation than with comparable oral doses of aminophylline and 40 times higher than with choline theophyllinate. The purpose of the present study, therefore, was to evaluate the clinical and electrocardiographic responses to the oral administration of theophylline in the vehicle of an elixir in patients with angina pectoris.

Material and Method. Our observations are based on the study of 30 ambulatory cases selected because of an established pattern of anginal episodes and known response to other forms of treatment. In all cases there was unequivocal benefit from both the prophylactic and therapeutic administration of nitroglycerin. The diagnosis had been clearly established by the patient's history, and in more than one-half of the cases electrocardiographic confirmation had also been obtained. Six of the 30 patients had sustained previous myocardial infarction while all of the remainder suffered from coronary heart disease without infarction. The anginal episodes were of a relatively mild nature in 16 patients, moderate in 8, and severe in 6. Only 5 cases had arterial hypertension; the rest had normal blood pressure. The ages ranged from

46 to 72 years with approximately one-third of the patients 60 years of age or older.

The elixir of theophylline (Elixophyllin*) was administered by mouth in doses of 3 tablespoonfuls 3 times daily, that is, on arising, at 3:00 P.M., and on retiring. Patients receiving a control elixir were given the same dosage of a liquid preparation identical to that of theophylline in color, smell, and taste. Both of the medicaments were administered by the "double-blind" method in which neither the patient nor the physician prescribing the drug and observing the clinical course knew the content of the preparations. Two equal groups of 15 cases (matched as evenly as possible with respect to age and severity of the disease) were treated, one with solution A (Elixophyllin) and one with solution B (control) for a period of 2 weeks. At the beginning of the third week, solution A was substituted for solution B and *vice versa*, and the patients were allowed to continue on the new preparation until the end of the fourth week of the experiment. The drugs were again switched every 2 weeks during the next 4-week period.

1) Effect on anginal pain: A record of the pain experience was kept in each instance by a notation at bedtime as to whether symptoms were the same as usual, unusually severe, exceptionally mild, or completely absent. The number of nitroglycerin tablets required daily to control the attacks was also recorded.

2) Effect on response to exercise: The Master two-step test was employed in 14 carefully selected patients. In each of these, control tests recorded from day to day revealed a relatively constant electrocardiographic response to measured exercise, characterized by ischemic ST segment depression and T-wave inversion. Moreover, in each instance sublingual administration of nitroglycerin immediately preceding the test prevented or favorably modified the abnormal pattern routinely observed in control studies. The number of ascents and descents of the two-step staircase was individualized according to the desired response and was kept constant for each patient. Thus, there was no adherence to a "single" or "double" test as defined by Master, Pordy and Chesky[16]. Electrocardiographic records were obtained by this means in all 14 patients while receiving either the control or theophylline preparation. One or the other of these agents was administered orally in a single dose of 5 tablespoonfuls before breakfast on consecutive mornings 15 minutes to 4 hours before the performance of exercise. In addition, exercise-electrocardiographic tests were also performed on the same patients while receiving intermittent doses of "placebo" and theophylline respectively, namely, 3 tablespoonfuls t.i.d. A total of 314 tests was obtained on the 14 patients studied by this technique. Measurement was made of the degree of ST segment depression observed in the post-exercise electrocardiograms with each of the two agents employed.

TABLE 1.—COMPARISON OF PAIN EXPERIENCE WITH PLACEBO AND THEOPHYLLINE (ELIXOPHYLLIN) EVALUATED BY "DAILY REPORT CARD" IN 30 PATIENTS WITH ANGINA PECTORIS

Agent	*Total no. days reported*	*Percentage of days in which cardiac pain was reported as*			
		Same as usual	*Less than usual*	*More than usual*	*None at all*
Placebo	832	57.6	31.7	7.3	3.4
Elixophyllin	830	18.9	54.8	5.1	21.2

Results. 1) Effect on anginal pain: Comparison of the responses to placebo and theophylline, as determined by the use of a "daily report card" in the 30 cases in the series, clearly established the superiority of the xanthine in the control of symptoms (Table 1). Thus, during treatment with placebo, only 35.1% of the patient-days were recorded as associated with "no pain" or "less pain" as compared with 76.0% of the patient-days during therapy with theophylline. In 16 of the 30 patients, the response was "good" or "excellent"

*Elixophyllin, supplied by Sherman Laboratories, contains 80 mg. of theophylline in each tablespoonful (15 ml.) dose. Alcohol is present in a concentration of 20% by volume.

during both courses of therapy with theophylline, while in no instance was a consistently favorable response observed with control medication.

2) Exercise-electrocardiographic tests: In 11 of the 14 patients repeatedly tested following single oral doses of 5 tablespoonfuls of the elixir of theophylline, the post-exercise electrocardiograms were considerably less positive than those observed following control medication. The protective influence of theophylline administered in this form and dosage appeared to have its onset in 20 to 30 minutes with a duration of action of at least 2 hours (Fig. 1). In 7 of the 11 "responsive" patients, the test was consistently normal, or nearly so, when performed at any time during the therapeutic activity of the drug. In these, the magnitude of the response was similar to that following nitroglycerin, but the duration of action was considerably more prolonged. In the remaining 4 "responsive" patients, the electrocardiographic records following exercise were mildly or moderately positive on some occasions during the therapeutic activity of theophylline but always less so than comparable records obtained after the administration of "placebo." After several days on maintenance doses of theophylline (3 tablespoonfuls t.i.d.) exercise-electrocardiographic tests showed similar striking differences as compared with those observed with control medication. Thus of 52 tests in 12 patients, an improved response was noted in 38 records.

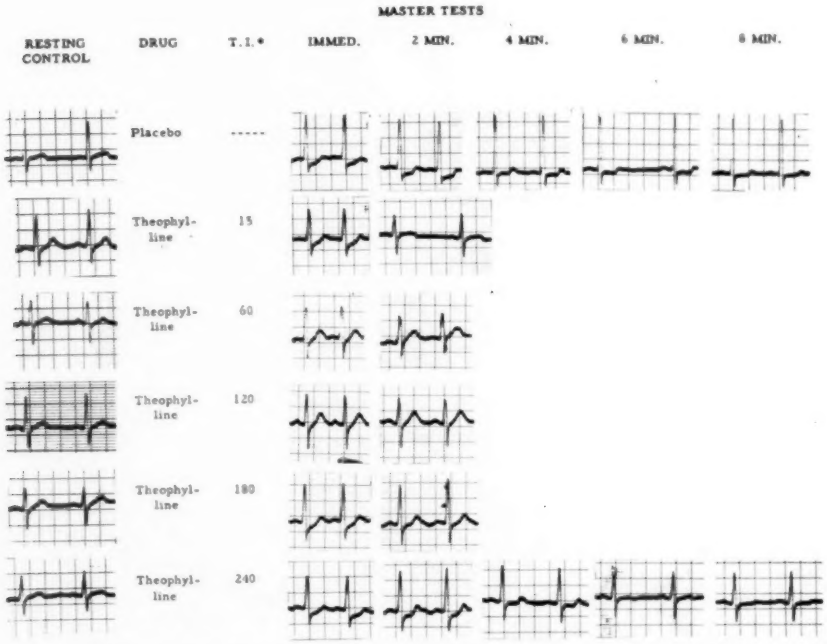

Fig. 1.—Master two-step tests in a patient with angina pectoris following placebo and a single 5 tablespoonful dose of an elixir of theophylline (400 mg.).
*T.I.—Time interval (minutes) between medication and beginning of test.

Discussion. The value of the xanthines in the treatment of coronary

artery disease has been a controversial subject since their introduction for this disorder almost 65 years ago. Not only is there sharp conflict regarding their therapeutic usefulness, but even the significance of their vasodilator effect on the coronary circulation in laboratory animals has been debated. Clinical evaluation has been hampered largely by the lack of objective methods for determining alterations in the pain-experience in patients with angina pectoris. Animal experimentation, however carefully performed, constantly raises the question of the possibility of species variations and whether or not the findings are applicable to man. The employment of "double-blind" clinical studies, while often effective in the elimination of bias, has certain distinct limitations (Russek[17]). During the past 15 years, therefore, we[21-29] have relied upon the evidence obtained from the electrocardiographic responses to standard exercise in carefully selected patients with established coronary artery disease.

Using this technique in earlier studies, we obtained clear evidence of favorable response to aminophylline administered intravenously but could not demonstrate similar benefit from usual therapeutic oral doses of the drug. It appeared evident, therefore, that the failure with oral therapy was correlated with sub-threshold blood theophylline levels from inadequate dosage or poor absorption from the gastrointestinal tract or both. Consequently, our interest has been stimulated by the recent introduction of other theophylline derivatives or preparations which are alleged to permit higher dosage, better absorption, and more effective blood levels than are possible with the use of aminophylline.

Our observations with an elixir of theophylline (Elixophyllin) utilizing doses of 3 tablespoonfuls 3 times daily (240 mg. of theophylline t.i.d.) clearly indicate that the drug exerts real benefit in the treatment of patients with angina pectoris. Not only was this demonstrated by "double-blind" studies designed to evaluate the modality of pain but, even more significantly, by objective measurements of the electrocardiographic response to measured exercise. From such observations in man, it can no longer be denied that theophylline and other xanthine derivatives may exert a favorable influence on coronary-myocardial relationship, despite observations suggesting the contrary in experimental animals. The clinical concept that these agents are "malignant vasodilators" since they increase cardiac work proportionately more than coronary flow is therefore no longer tenable. Moreover, in the light of these findings, other derivatives and preparations of the xanthine group should be fully explored to permit increased use of these agents in the management of coronary artery disease. At present it appears clear that the most favorable response with oral administration is obtained with theophylline in hydroalcoholic solution. Obviously the effectiveness of this preparation is based not on dosage, since equal amounts of other xanthines have proved of little value, but on rapid absorption and the attainment of high blood levels made possible by the vehicle employed. Our observations in other studies in progress, using this preparation of theophylline, have confirmed its value in the treatment and prevention of the acute asthmatic attack (Burbank, Schluger and McGinn[5], Greenbaum[11], Kessler[12], Spielman[33]) and have indicated its ability to enhance diuresis from mercurial agents in patients becoming refractory to such therapy.

In addition to the use of nitroglycerin for the acute anginal episode, there

are now three effective long-acting preparations from which more than placebo effect can be expected in the treatment of angina pectoris. Our investigation of countless preparations over the past 15 years has clearly shown that only pentaerythritol tetranitrate (PETN), erythrol tetranitrate (ETN), and the hydro-alcoholic solution of theophylline (Elixophyllin) employed in this study, are capable of producing favorable clinical and electrocardiographic response in this disorder. Although papaverine was also found to exert benefit, the high dosage required, as well as the associated side-effects from the drug, have precluded its use in routine management.

As with the nitrites, the exact mode of action of the xanthines remains unknown. This is because present methods do not permit accurate assessment of the relative role of changes in coronary flow, myocardial efficiency, cardiac load, or pressor amine activity (myocardial) in the observed clinical response.

Summary. Despite the continuing popularity of the xanthines in the treatment of angina pectoris, experimental observations appear to indicate that these agents increase cardiac work proportionately more than coronary flow and thus are "undesirable coronary vasodilators." While many investigators have failed to discern a favorable clinical response to aminophylline administered orally in carefully designed studies, the unequivocal benefit obtained from its intravenous administration remains unchallenged. Consequently, inadequate blood theophylline levels resulting from gastric intolerance and poor absorption appear responsible for the lack of clinical response to oral therapy.

The present study has shown that a hydro-alcoholic solution of theophylline (Elixophyllin), administered orally to 30 patients with angina pectoris, was strikingly effective not only in the control of symptoms but in its modifying action on the electrocardiographic response to standard exercise. The efficacy of this preparation is based on the rapid absorption and attainment of high blood levels made possible by the vehicle employed. In the light of these findings, conclusions derived from animal experiments, which have classified theophylline as a "malignant coronary vasodilator," must be rejected for man.

Xanthine derivatives, both by the intravenous and oral route, should be reinstated as valuable agents in the treatment of angina pectoris and other coronary disease states. At the present time, the most effective preparation for oral administration is a hydro-alcoholic solution of theophylline, but other derivatives and preparations of the xanthine group should be fully explored to permit their increased use in the management of coronary heart disease.

ACKNOWLEDGMENT: Thanks are due to Dr. Frank P. Panzarella for suggesting the present study.

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SUMMARIO IN INTERLINGUA

Es le Xanthinas Efficace in le Tractamento de Angina de Pectore?

In despecto del continue popularitate del xanthinas in le tractamento de angina de pectore, observationes experimental pare indicar que iste agentes augmenta le labor cardiac proportionalmente plus que le fluxo coronari e assi es indesirabile "vasodilatatores coronari." Durante que multe investigatores ha notate nulle favorabile responsa clinic a aminophyllina in administration oral sub le conditiones de cautèmente planate studios, le beneficio inequivoc obtenite ab le administration intravenose de iste agente remane sin dementi. Per consequente, inadequate nivellos de theophyllina in le sanguine como resultato de non-tolerantia gastric e imperfecte absorption pare esser responsabile pro le absentia de responsa clinic in therapia oral.

Le presente studio ha demonstrate que un solution hydro-alcoholic de theophyllina (Elixophyllina), administrate per via oral a 30 patientes con angina de pectore, esseva frappantemente efficace non solmente in su capacitate de supprimer le symptomas sed etiam in su action modificatori super le responsa electrocardiographic a exercitios standard. Le efficacia de iste preparato es conditionate per le rapide absorption e le resultante alte nivellos de illo in le

(Continued on page 174)

THE TREATMENT OF ANGINA PECTORIS WITH A NEW PROLONGED ACTION PENTAERYTHRITOL TETRANITRATE*

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Nitroglycerine, used as early as 1876 in the treatment of heart disease, has become one of the most commonly employed drugs in the management of angina pectoris (Plotz[3]). Its judicious use, often in combination with small doses of sedatives or tranquilizers, enables the great majority of angina patients to lead useful and comfortable lives.

Unfortunately, the body speedily dissipates the benefit derived from nitroglycerine, and the patient, as a result, usually has two additional burdens. First, he must take larger doses, which may add up to as many as 20 to 30 tablets daily. Even where the number of tablets taken is considerably less, he may still feel that he is a "drug addict" despite reassurance from his physician. This prevalent attitude seriously lessens the efficacy of treatment. Then again, unless he has mastered the art of taking the medication before anginal pain occurs, the patient waits until he actually has pain before starting treatment, which then has no prophylactic effect. A number of patients have a third problem in their inability to prevent nocturnal attacks.

In recognition of these drawbacks in the use of short-acting nitroglycerine, clinicians have investigated the value of longer acting drugs, whose effects depend on their slow release of nitrites. Most of these, however, have little merit, and include, among others, sodium nitrite, bismuth subnitrate, and mannitol hexanitrate. Sodium nitrite may even be harmful to some patients with heart disease (Master, Jaffe and Dack[2]).

Easily the best of the drugs for the prophylaxis of angina is pentaerythritol tetranitrate (PETN), first introduced into clinical medicine for the treatment of angina pectoris in this country in 1952 (Plotz[4], Talley, Beard and Doherty[5]). Experience since that date has widened our knowledge of this drug's action and usefulness and has confirmed our first good impressions. Its use reduces the patient's dependence on nitroglycerine and he is gratified to find that he is able to prevent the onset of seizures rather than being compelled to await, usually with great apprehension, for the beginning of pain. Two types of angina, angina decubitus and postprandial pain, are especially helped.

PETN, which is usually given in 10- to 20-mg. tablets 3 or 4 times daily, has one important drawback in mild or moderate cases. If a patient with mild angina has been taking only one or 2 tablets of nitroglycerine a day, and substitutes 3 PETN tablets, it must certainly appear to him that he is taking more rather than less medication.

This paper describes clinical experience with a new sustained action cap-

*This study was conducted under a grant from the New Drug Institute, Inc., New York, New York.

sule containing many tiny pellets of PETN*. All pellets release their medication by a leeching process over 8 to 10 hours providing effective drug levels for 12-hour periods. The pellets are specially coated with a plastic semipermeable membrane that requires only moisture to dissolve them. Since release of the active medication is not dependent on gastrointestinal motility or pH levels, both of which vary considerably, the new capsules overcome problems of release frequently associated with other sustained release medications.

Material and Methods. The drug was administered for up to 12 weeks to 50 patients with unequivocal angina pectoris resulting from organic heart disease. A mere clinical story of angina pectoris, no matter how typical, was considered insufficient to warrant inclusion of an individual in the test series. In all instances, therefore, electrocardiographic evidence of myocardial involvement served as the objective basis for the diagnosis and the selection of patients. The basal electrocardiograms of 3 of the patients were normal, but their responses to the exercise tolerance test were typical of myocardial ischemia. Of the 50 patients, 49 had coronary heart disease and one had rheumatic heart disease (aortic stenosis). Among those with coronary heart disease, 25 previously had one or more, well-documented major episodes of infarction. Several of the other 24 had objective evidence of heart disease as shown by roentgenogram in addition to the electrocardiogram.

A second basis for selection, adhered to in 48 cases, was that the patient be a regular user of nitroglycerine. Since, however, a small percentage of persons with true angina do not receive benefit from nitroglycerine, 2 such patients were included in this series to explore the therapeutic range of Duotrate.

Three criteria were established to evaluate the merit of the new sustained-action capsule of PETN: (1) whether it gave relief from angina pectoris, as determined in 12 patients who received it and a placebo capsule in alternate weeks, while taking nitroglycerine; (2) whether it permitted reduction of nitroglycerine tablet intake by at least one-third; and (3) whether it gave greater relief than conventional, more rapidly acting tablets containing 10 or 20 mg. of PETN, given 3 times daily. The dosage of Duotrate, containing 30 mg. of PETN per capsule, was twice daily for 45 patients and 3 times daily for the other 5.

Course and Results. Thirty-eight patients (76%) had highly satisfactory results from Duotrate as evaluated by the rigid criteria stated. All had considerable relief from angina, all had a reduction of at least one-third in the number of nitroglycerine tablets required, all had greater relief with Duotrate than with PETN tablets. Each patient expressed willingness to continue with the Duotrate regimen rather than the drug they had used prior to the test period. Two more patients satisfied most of these criteria but preferred to continue with plain PETN tablets.

Of the 10 remaining patients, the 2 who had no relief with nitroglycerine received no benefit from either form of PETN, despite the unquestionable existence of angina pectoris resulting from coronary artery disease. A third patient discontinued Duotrate because of "light-headedness" which he said did not occur with small doses of nitroglycerine carefully controlled and frequently repeated. The remaining 7 patients reported they had more relief with either nitroglycerine or plain PETN tablets.

Two patients died during the test period from causes unrelated to the study. Postmortem examinations were available in each case. One patient had a fresh posterior infarction in addition to an old anterior lesion. The other had aortic stenosis with cerebral infarct. Both patients, however, had been taking Duotrate long enough for a definite therapeutic pattern to be evident, and are included in this series.

*Duotrate Plateau Caps, supplied through the courtesy om Marion Laboratories, Inc., Kansas City, Missouri.

PLACEBO CONTROL. Two of the 12 patients reported a slight reduction (less than 10%) in the amount of nitroglycerine needed. The others had not the slightest relief with the placebo capsule and were able to distinguish easily between the blank and Duotrate.

NUMBER OF TABLETS. For the 38 patients with highly satisfactory results, the range in reduction of number of nitroglycerine tablets was 33 to 100%. Two patients experienced complete relief with Duotrate alone, requiring none of their usual 12 to 15 nitroglycerine tablets weekly. In 6 other patients who had been taking 14 to 21 nitroglycerine tablets weekly, the effect of Duotrate was almost as powerful, since they needed no nitroglycerine during some weeks and only 3 to 7 tablets during others. As a further illustration of results, 4 patients ordinarily requiring 7 to 25 nitroglycerine tablets weekly obtained relief on Duotrate and the addition of just 1 to 5 nitroglycerine tablets weekly. In severe cases, the necessary minimum of 70 to 100 nitroglycerine tablets a week fell dramatically to 10 to 60 tablets. The total number of weekly nitroglycerine tablets and Duotrate capsules taken during the test period was less than the previous number of nitroglycerine tablets in 15 patients, particularly the severer cases.

FLEXIBILITY OF DOSAGE SCHEDULE. Initially, all patients received a 30-mg. capsule of Duotrate twice a day, on arising and before the evening meal. It was subsequently discovered that varying the time of administration of the second dose proved more satisfactory in some instances. If angina was troublesome in the late afternoon, the second dose could be given earlier, sometimes at 3 P.M. If nocturnal angina was present, it was advantageous to give the second dose on retiring. In 5 cases of severe angina, a third dose was given late at night with beneficial results. The increased dosage did not increase the incidence of side reactions.

Further flexibility of dosage was provided by combining Duotrate with the administration of other medications, most often nitroglycerine. A few patients with mild angina were able to get along with Duotrate alone, but, as in the case with PETN in any form, many patients are more comfortable with supplementary nitroglycerine. A very few patients added one dose of plain PETN a day. Most commonly, as in the case of any nitrite drug, the patient had more relief when small doses of phenobarbital or meprobamate were added.

SIDE REACTIONS. Eleven patients who previously had side reactions from drugs in the nitrite series had similar symptoms with the new capsule. The reactions were temporary in 10 patients, disappearing during the course of treatment. In only one patient was the reaction troublesome enough to require the discontinuance of the medication.

Eight patients complained of giddiness, light-headedness or mild vertigo, including the one who terminated treatment. Two others complained of mild palpitation during the first few days only. The last patient was troubled by both types of symptoms. The symptoms subsided in all instances and the test period was terminated without further difficulty.

Discussion. The results of this clinical study of 50 patients treated with a new sustained-action form of pentaerythritol tetranitrate (Duotrate) confirm our opinion that it is the best nitroglycerine-sparing drug available for the treatment of angina pectoris. There is some reason to believe that it may have other beneficial effects in the treatment of coronary disease (Kissane, Fidler and Conn[1]), although

these were not investigated in this study.

The flexible dosage schedule and the negligible side reactions with Duotrate significantly increased the opportunity to individualize therapy, an important factor in making the lives of angina patients more useful and comfortable. In addition, most patients preferred the morning dose of Duotrate to 3 tablets of PETN taken during the day. The morning capsule removed a psychological handicap, because the patient felt more secure, knowing that he had taken his "medication for the day."

In general, equal amounts of PETN, no matter how given, are equally effective in relieving anginal seizures. On the other hand, the patient usually judges acceptability in terms of ease of administration, the number of times he must take the medication, the reduction in number of nitroglycerine tablets needed, and the type and degree of side reactions, if any. Under these criteria, Duotrate is a valuable addition to our present therapeutic armamentarium.

Summary. A new sustained-action capsule form of pentaerythritol tetranitrate (PETN), depending for its release on the action of water rather than gastrointestinal motility or pH levels, was studied in 50 patients with classical angina pectoris, 48 of whom were regular users of nitroglycerine. The new medication, Duotrate, enabled 38 (76%) patients to reduce their intake of nitroglycerine by at least one-third, or eliminate it completely. Side reactions were few and for the most part, negligible. The dosage schedule was flexible and allowed therapy to be administered on an individual basis. A large percentage of patients preferred the new regimen to all previous ones.

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SUMMARIO IN INTERLINGUA

Le Tractamento de Angina de Pectore con un Nove Tetranitrato de Pentaerythritol a Action Prolongate

Un nove tetranitrato de pentaerythritol in forma de capsulas, con un action prolongate dependente de su liberation per le action de aqua plus tosto que del motilitate gastrointestinal o del nivello de pH, esseva studiate in 50 patientes con classic angina de pectore. Quaranta-octo del 50 esseva usatores regular de nitroglycerina. Le nove medication, Duotrate, permitteva a 38 del patientes (76%) reducer lor ingestion de nitroglycerina per al minus un tertio o eliminar lo completemente. Le reactiones lateral esseva pauco numerose e generalmente negligibile. Le dosage esseva flexibile e rendeva possibile le administration del therapia super un base individualisate. Un alte procentage del patientes prefereva le nove regime a omnes previemente usate per illes.

EFFECT OF FOOD ON ABSORPTION OF A NEW FORM OF ERYTHROMYCIN PROPIONATE*

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In a recent study (Hirsch and Finland[2]) it was shown that the absorption of erythromycin propionate in capsules and of erythromycin stearate in coated tablets was markedly reduced when given immediately after a meal. A single dose of 500 mg. of either of these erythromycin preparations given before breakfast produced much greater activity in the serum than a similar dose (all as base equivalents) of triacetyloleandomycin in capsules given either before or after breakfast; this was true when the activity was measured by any of 4 methods, namely, as antistreptococcal or antistaphylococcal activity in the serum determined in a broth-dilution method or as concentrations of either erythromycin or oleandomycin determined by the cup-plate assay with *Sarcina lutea*. This advantage of erythromycin propionate was lost when the dose was given immediately after the meal.

After that study was completed, a new preparation of erythromycin propionate in the form of its lauryl sulfate compounded with excipients into coarse granules was made available; this preparation, after adding water and shaking produced a palatable, pleasantly flavored suspension the absorption of which, in preliminary trials, appeared to be unaffected by food (Griffith[1]). The present study was undertaken to determine the effect of a meal on the absorption of erythromycin from this preparation.

Materials and Methods. The new preparation of the lauryl sulfate salt of propionyl erythromycin ester was provided by Eli Lilly & Co. as "Ilosone Compound 31979" in screw capped bottles. The addition of 48 ml. of water to the contents of one bottle yielded, after thorough shaking, a uniform suspension that contained 125 mg. equivalent of erythromycin in each 5 ml. The desired doses were carefully measured out and given with a convenient amount of water.

Three groups of subjects were used in a crossover study with the same single dose of the drug given on one occasion on a fasting

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†With the technical assistance of Clare Wilcox and Joan Yarrows and the cooperation of Dr. Karl V. Quinn, Superintendent, Wrentham State School.

stomach and on the other immediately after breakfast; the individual doses were separated by an interval of at least 4 days. Eight normal young men (average weight 82 kg.) were given doses of 500 mg. (erythromycin equivalent) and 2 groups of 6 children (aged 2 to 3 years and 8 to 9 years respectively) were given single doses of 10 mg. per kg. of body weight. In the adults blood was drawn before and again 1, 2, 4, 8 and 12 hours after each dose. In the children bloods were drawn at 1, 3 and 8 hours after each dose and immediately before the second dose. When the dose was given on a fasting stomach, breakfast was withheld in the adults until after the 2-hour blood was drawn, and in the children until the 3-hour sample was obtained. The serums were promptly separated and stored at −20° C. until the entire study was completed. All sera from the same subject were assayed simultaneously for antibacterial activity by a two-fold dilution test using both *Streptococcus 98* and *Staphylococcus 209P*. The activity of each serum was expressed as the maximum dilution of serum which inhibited the test organism. "Total activity" from any given dose was estimated for the period of study by calculating the "area" under the curve of serum levels (number of 2-fold inhibiting dilutions × number of hours) and expressed as "dilution-hours." Control assays of the sensitivity of the test strains were carried out in broth with a standard solution of erythromycin during each day's tests; *Strep. 98* was inhibited by 0.02 μg. per ml. and *Staph. 209P* by 0.2 μg. per ml. on each of 4 days and by twice these amounts on one day.

Results. The results of all the assays are summarized graphically in Fig. 1 and the average values for the levels of activity at the different intervals,

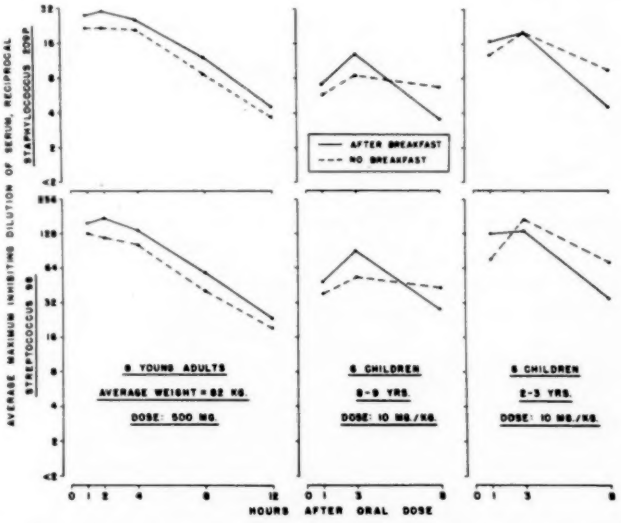

Fig. 1.—Antibacterial activity in serum of 3 groups of subjects after ingestion of the same dose of monopropionyl erythromycin lauryl sulfate on a fasting stomach and immediately after breakfast.

the peak levels and "total activity" in the serum are shown for the adults in Table 1 and for both groups of children in Table 2. All control sera obtained before the doses failed to inhibit either test organism. In the adults all of the average values obtained from the post-breakfast dose, were slightly higher than those resulting from fasting dose, but none of these differences was significant ($P>0.05$ in every instance).

In the older children, the dose given after the meal produced higher average

levels of activity at 1 and 3 hours and lower levels at 8 hours as compared with those resulting from the fasting dose. In the younger children the same was true except that at 3 hours the average levels were essentially the same. However, none of the differences was statistically significant and, moreover, the average peak levels and total activity obtained in both groups of children were essentially the same for the doses given before and after breakfast.

When the results in the 2 groups of children are compared, the average antistreptococcal and antistaphylococ-

TABLE 1.—COMPARISON OF ANTIBACTERIAL ACTIVITY OF SERUM OF 8 NORMAL MEN AFTER SINGLE ORAL DOSES OF 500 MG. OF A SUSPENSION OF THE LAURYL SULFATE SALT OF ERYTHROMYCIN PROPIONATE GIVEN ON A FASTING STOMACH AND IMMEDIATELY AFTER BREAKFAST

		*Average Antibacterial Activity of Serum**							
		Hours After Dose						*Peak Level*	*Total Activity*
Test Organism	*Relation to Meal*	*0*	*1*	*2*	*4*	*8*	*12*	*± SD*	*First 12 Hr.†*
Strep. 98	before‡	0	7.0	6.9	6.7	5.3	4.3	7.1 ± 0.7	67 ± 8.5
	after	0	7.3	7.4	7.1	5.9	4.6	7.5 ± 0.5	73 ± 5.3
Staph 209P	before	0	4.4	4.4	4.4	3.1	1.9	4.6 ± 0.6	40 ± 8.5
	after	0	4.8	4.9	4.7	3.6	2.2	4.9 ± 0.3	45 ± 5.3

The differences in the values before and after the meal were not significant for the peak levels and total activity with either test organism ($P > 0.05$ in every instance).

*Expressed as a maximum number of two-fold dilutions of serum which inhibited the test organism.
†"Area" under the blood level curves expressed as dilution-hours (maximum number of two-fold inhibiting dilutions x number of hours).
‡Breakfast taken 2 hours after the dose.

TABLE 2.—ANTIBACTERIAL ACTIVITY OF SERUM OF TWO GROUPS OF CHILDREN AFTER SINGLE ORAL DOSES OF 10 MG PER KG. OF THE LAURYL SULFATE SALT OF ERYTHROMYCIN PROPIONATE GIVEN ON A FASTING STOMACH AND IMMEDIATELY AFTER BREAKFAST

			Average Antibacterial Activity of Serum† ± SD					
			Hours After Dose					
*Groups**	*Test Organism*	*Relation to Breakfast*	*0*	*1*	*3*	*8*	*Peak Level*	*Average Total Activity First 8 Hours‡ ± SD*
I	Strep. 98	before§	0	6.3 ± 1.7	7.4 ± 2.0	6.2 ± 1.3	7.5 ± 1.8	51 ± 11.8
		after	–	7.0 ± 2.0	7.1 ± 1.1	5.2 ± 0.8	7.4 ± 1.0	48 ± 7.1
	Staph. 209P	before	0	3.7 ± 2.1	4.3 ± 1.8	3.3 ± 1.6	4.7 ± 1.5	29 ± 12.2
		after	–	4.1 ± 2.0	4.3 ± 1.2	2.2 ± 1.0	4.6 ± 1.0	27 ± 6.4
II	Strep. 98	before	0	5.3 ± 1.5	5.8 ± 2.0	5.4 ± 1.2	6.6 ± 1.3	42 ± 10.4
		after	–	5.6 ± 1.4	6.5 ± 0.8	4.8 ± 1.4	6.6 ± 0.8	43 ± 5.6
	Staph. 209P	before	0	2.5 ± 1.6	3.1 ± 1.2	2.8 ± 1.3	3.9 ± 1.1	21 ± 9.8
		after	–	2.8 ± 2.4	3.7 ± 0.9	1.8 ± 1.5	3.9 ± 1.1	22 ± 5.3

Differences between average values before and after the meal were not significant at each interval at the peak levels and for total activity assayed with each test strain; also none of the differences between corresponding values in groups I or II were statistically significant ($P > 0.05$ in every instance).

*I = 6 children 2 to 3 years old; II = 6 children 8 to 9 years old.
†Expressed as maximum number of two-fold dilutions of serum which inhibited the test organism.
‡Equivalent to "area" under curve of serum levels expressed as "dilution-hours" (maximum number of two-fold inhibiting dilutions x number of hours).
§Breakfast given 3 hours after the dose.

cal activity at each interval, at the peak and for the entire 8-hour period was higher in each instance in the younger than in the older ones, although the same dose, on a body weight basis, was given to both groups. None of these differences, however, was significant ($P>0.05$ in every instance). Comparisons of these results with those obtained in the groups of adults was not feasible as a uniform dose of 500 mg. was given to the latter.

TABLE 3.—COMPARISON OF RESULTS OBTAINED IN ADULTS IN THE PRESENT STUDY WITH THOSE PREVIOUSLY REPORTED* IN A SIMILAR STUDY IN WHICH 500 MG. OF ERYTHROMYCIN PROPIONATE WAS GIVEN IN CAPSULES

	Form of Erythromycin Propionate	*Relation to Breakfast*	*Average Antibacterial Activity in Serum*			
			Against Strep. 98		*Against Staph. 209P*	
			Peak Level†	*Total Activity First 12 Hours*‡	*Peak Level*†	*Total Activity First 12 Hours*‡
A	Suspension	before	7.1 ± 0.7	67 ± 8.5	4.6 ± 0.6	40.4 ± 8.5
B		after	7.5 ± 0.5	73 ± 5.3	4.9 ± 0.3	44.9 ± 5.3
C	Capsule*	before	7.5 ± 0.8	62 ± 11.9	4.2 ± 0.8	31.4 ± 10.3
D		after	5.2 ± 0.8	37 ± 7.3	2.3 ± 0.6	11.1 ± 4.9
	Differences		*"P" values*			
	A–C		>0.05	>0.05	>0.05	>0.05
	B–C		>0.05	<0.05	<0.05	<0.01
	A–D		<0.001	<0.001	<0.001	<0.001
	B–D		<0.001	<0.001	<0.001	<0.001

*Hirsch and Finland[2]; "total activity" was reported for 24 hours, but data given here have been calculated for 12 hours.

†Expressed as maximum number of two-fold dilutions inhibiting ± standard deviation.

‡Expressed as area under the curves of serum levels in dilution-hours ± standard deviation.

It was, however, of interest to compare the results obtained in the adults following the doses of the suspension in the present study with those previously reported after administration to comparable subjects of a similar dose of erythromycin propionate in gelatin capsules (Hirsch and Finland[2]). For this purpose the average peak levels and total activity for the first 12 hours may be used and these comparisons are shown in Table 3. There were some differences in the values obtained when the 2 preparations were given before breakfast, but none of these differences (A-C) was significant. Also, the average peak level of antistreptococcal activity obtained with the suspension after the meal was the same as from the capsule taken before breakfast, but the peak antistaphylococcal level and the average total activity against both the streptococcus and the staphylococcus resulting from the post-breakfast dose of the suspension were all greater than from the premeal dose of the capsules, and each of these differences (B-C) was significant. Finally, as may be expected, the suspension given either fasting (A) or after breakfast (B) produced greater peak and total activities against both the streptococcus and staphylococcus when compared with those produced by the capsules given after breakfast (D); all of these differences (A-D and B-D) were highly significant ($P<0.001$ in each instance).

Discussion. The literature dealing with the absorption of oral preparations of erythromycin and oleandomy-

cin and the effect of food on that absorption was reviewed in the previous paper (Hirsch and Finland[2]). The data presented in that paper and in the others that were quoted there indicated that erythromycin propionate given on an empty stomach yielded significantly higher levels of antibacterial activity in the blood than base-equivalent amounts of any of the other forms of erythromycin or oleandomycin with which it has been compared; however, much of this advantage was lost when the erythromycin propionate was given in gelatin capsules immediately after a meal. This was particularly true in comparisons with triacetyloleandomycin, the absorption of which was only somewhat delayed but not depressed by the meal. The new suspension of the lauryl sulfate salt of erythromycin propionate, when given after a meal appears to be absorbed at least as well as when given before the meal and possibly even slightly better than the form in the gelatin capsule when given on an empty stomach. The last comparison, however, requires confirmation by direct comparison in the same subjects.

Summary and Conclusions. Crossover studies of the absorption of a new preparation of erythromycin propionate in the form of its lauryl sulfate in granules that make a palatable aqueous suspension were carried out in 3 groups of subjects: 8 young adults, 6 children 2 to 3 years old, and 6 children 8 to 9 years old. In each of these groups, the levels of antistaphylococcal and antistreptococcal activity provided by single doses given immediately after breakfast were not significantly different from those obtained when the same dose was given on a fasting stomach. Comparisons with the results of previous studies suggest that, with respect to the antibacterial activity it produces in the serum, the new preparation is superior to any previous preparations of either erythromycin or oleandomycin that have been studied in a comparable manner.

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SUMMARIO IN INTERLINGUA

Le Effecto de Alimentos Super le Absorption de un Nove Forma de Propionato de Erythromycina

Esseva studiate le absorption de un nove preparato de propionato de erythromycina in le forma de su sulfato laurylic in granulos que produce un palatabile suspension aquose esseva effectuate in 3 gruppos de subjectos: 8 juvene adultos, 6 juveniles de inter 2 e 3 annos de etate, e 6 juveniles de inter 8 e 9 annos de etate. In omne iste gruppos, le nivellos del activitate antistaphylococcal e antistreptococcal que resultava de un dose unic administrate immediatemente post le jentaculo non differeva significativemente del nivellos de ille activitate quando le mesme dose esseva administrate in stato jejun. Comparationes con le resultatos de previe studios suggere que, con respecto al activitate antibacterial producite per illo in le sero, le nove preparato es superior a omne previe preparato tanto de erythromycina como etiam de oleandomycina in tanto que illos ha essite studiate in un maniera comparabile.

SEROTONIN DEGRADATION BY CERULOPLASMIN AND ITS INHIBITION BY ISONIAZID AND IPRONIAZID*

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On the basis of certain clinicopathologic observations, it was recently postulated that fibrosis might result from a deranged interaction of serotonin-amine oxidase mechanisms at the tissue level (Zarafonetis, Lorber and Hanson[10,11]). It was theorized that fibrosis would ensue whenever an excess serotonin effect was sustained over a sufficient period of time. This could result from a relative imbalance between the amount of serotonin present locally and the rate of its degradation. Accordingly, a series of studies were initiated which were designed to test this hypothesis. The present report deals with an investigation of the degradation of serotonin by human ceruloplasmin, and inhibition of this effect by both iproniazid (Marsilid) and isoniazid (Rimifon).

Materials and Methods. Serial 2-fold dilutions of ceruloplasmin preparations were made in physiological saline solution. The enzyme concentration which was found to metabolize between 2/3 and 3/4 of the serotonin-creatinine sulfate (300 μg.) was used in the final test system. This degree of enzyme activity was found to be present in a 1:40 dilution of the human ceruloplasmin designated "Kabi 831 DwZ 19," which contained 5.05 μg. of copper. A similar amount of enzyme activity was present in a 1:10 dilution of the second lot of ceruloplasmin employed, that is, "Kabi DwZ 37" which contained 17.6 μg. of copper.† The effect of pH on serotonin degradation by ceruloplasmin was determined by performing the assays at pH values ranging from 6.8 to 7.5.

PROCEDURE. To a 20-ml. beaker were added 1.0 ml. of the ceruloplasmin solution: 1.0 ml. of 0.5 M phosphate buffer, pH 7.4; and 0.5 ml. of the solution containing substances being tested for reaction inhibition (isoniazid,‡ iproniazid‡). Distilled water was added in place of inhibitor solution in the controls. The beakers were preincubated on a Dubnoff metabolic shaker for 15 minutes, following which 1 ml. of solution containing 300 μg. of serotonin creatinine sulfate was added. Final concentrations in the incubation mixture were 4.9×10^{-4}M for serotonin and 1×10^{-3}M for each inhibitor. The incubation was continued for 1 hour, and determinations for residual serotonin were made by the colorimetric method of Udenfriend, Weissbach and Brodie[8]. Controls included tests with boiled ceruloplasmin, and for color interference, the recovery of serotonin after incubation with isoniazid and iproniazid in the absence of enzyme.

Chromatographic confirmation of the experimental results was also undertaken. The

*This investigation was aided by a grant from the Pennsylvania Trudeau Society.

†Data on the copper content and other characteristics of the ceruloplasmin used in this study were provided by the Kabi Co., Stockholm, Sweden. The ceruloplasmin itself was generously made available by the Wyeth Laboratories, Radnor, Pa.

‡Isoniazid (Rimifon) and iproniazid (Marsilid) were kindly provided by Hoffmann-LaRoche, Inc., Nutley, N.J.

incubation mixtures were extracted by the method of Udenfriend, Weissbach and Brodie[8]. One hundred and fifty microliter aliquots of the final incubation extracts were placed on Whatman #1 filter paper for ascending chromatography. An isopropanol-ammonia-water solvent (100:1:2) was utilized and the color was developed with Ehrlich's reagent as described by Jepson[1].

Results. Figure 1 shows the characteristic response observed in these studies. It can be seen that ceruloplasmin of human origin readily degraded serotonin at pH 7.4. Both isoniazid and iproniazid, however, strongly inhibited the effect of ceruloplasmin on serotonin at physiologic pH. These findings were confirmed by chromatography.

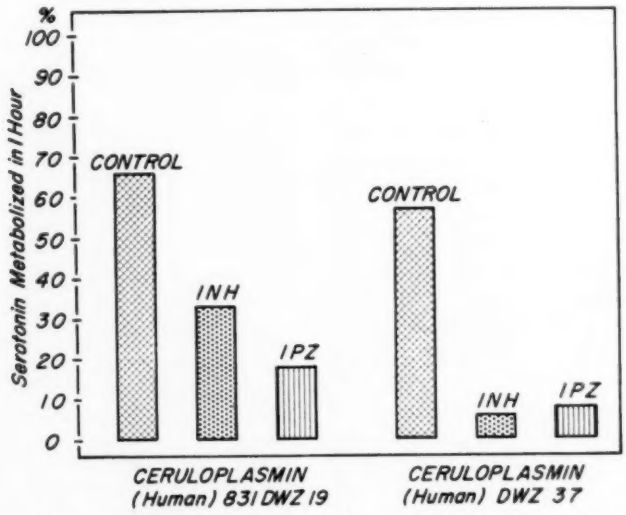

Fig. 1.—Effect of isoniazid (INH) and iproniazid (IPZ) on the degradation of serotonin by 2 lots of human ceruloplasmin. Experiments performed at pH 7.4.

Discussion. The finding that serotonin is metabolized in the presence of ceruloplasmin is in keeping with the observations of Porter and his associates[5]. These workers were the first to study the oxidation of serotonin in the presence of this enzyme. Their findings suggested that 2 consecutive oxidation steps occur in the metabolism of serotonin by ceruloplasmin. Since ceruloplasmin has no monoamine oxidase activity, they emphasized that this oxidative pathway might bear a relationship to the physiologic activity of serotonin. A similar suggestion was made by Martin, Ericksen and Benditt[4] who observed that serum from normal and pregnant humans oxidized 5-hydroxytryptamine. That ceruloplasmin oxidizes serotonin has also been observed by Sankar[7].

From the foregoing, it appears well established that oxidation in the presence of ceruloplasmin offers a pathway for the metabolism of serotonin other than that which involves amine oxidase transformation to 5-hydroxyindoleacetic acid (Udenfriend, Titus and Weissbach[9]). Our observation that both isoniazid and iproniazid inhibit the oxidative pathway of ceruloplasmin may be relevant to certain clinical observations. In this connection it may be noted that significant psychopharmacologic effects have been attributed

to monoamine oxidase inhibitors. The effects of iproniazid, for example, are believed to be due to its strong inhibitory action on monoamine oxidase activity (Zeller *et al.*[12]). While the physiologic and other effects of iproniazid may be largely due to amine oxidase inhibition, it seems reasonable to conclude that its inhibition of the ceruloplasmin oxidative pathway would also contribute significantly to the effects of this compound.

It is of interest, moreover, that isoniazid has similar, though less marked, clinical effects. Those actions have not been considered heretofore to be serotonin-related, however, since isoniazid does not inhibit monoamine oxidase activity. The finding that the destruction of serotonin by ceruloplasmin can be inhibited by isoniazid opens the way for re-interpretation of many clinical data on the effects of this substance.

Finally, the possible relationship of serotonin and these pathways of degradation and their inhibition to the fibrosis hypothesis remains to be elucidated. It may be noted, however, that excess serotonin, as in the carcinoid syndrome (Zarafonetis, Lorber and Hanson[11]), or experimentally injected (MacDonald, Robbins and Mallory[3]), leads to fibrosis. On the other hand, there is also evidence that the use of inhibitors of serotonin metabolism is associated with increased fibrosis. For example, in animals treated with Marsilid, experimental wounds showed much greater organization and fibrosis about the scar than did the wounds of the untreated controls (Reynolds *et al.*[6]). Moreover, careful histologic studies of tissues from patients with tuberculosis have shown more fibrous proliferation about healed tubercules in isoniazid-treated subjects than was found about tubercules from untreated or streptomycin-treated patients (Loring and MacVandiviere[2]). Thus, the hypothesis which originally included only the possible role of monoamine oxidase inhibitors in producing an excess local serotonin effect now must be broadened to include inhibition of the oxidative pathway of ceruloplasmin, and remain open to the possible addition of other channels of serotonin degradation. Further investigations in connection with this concept are underway in this laboratory and will be the subject of future reports.

Summary and Conclusions. 1. The degradation of serotonin by human ceruloplasmin has been confirmed.

2. This pathway of serotonin oxidation is strongly inhibited by both isoniazid and iproniazid.

3. The psychopharmacologic and other clinical effects of iproniazid thus probably reflect not only its inhibition of monoamine oxidase activity, but also its inhibition of ceruloplasmin oxidation of serotonin. Isoniazid, on the other hand, appears only to inhibit the latter pathway.

4. Possible implications of these findings with regard to a concept of fibrosis are also discussed.

ACKNOWLEDGMENTS: The authors wish to express their appreciation to Mrs. Shirley Pinto, Mrs. Claire Graff and Mrs. Natalie Bohi for their technical assistance during the course of this study.

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SUMMARIO IN INTERLINGUA

Le Degradation de Serotonina per Ceruloplasmina e Su Inhibition per Isoniazido e Iproniazio

1. Le degradation de serotonina per ceruloplasmina human ha essite confirmate.

2. Iste itinerario de oxydation de serotonina es fortemente inhibite tanto per isoniazido como etiam per iproniazido.

3. Le effectos psychopharmacologic de iproniazido e etiam le altere effectos clinic de iste agente reflecte assi probabilemente non solmente le facto que illo inhibi le activitate de oxydase de monoamina sed etiam le facto que illo inhibi le oxydation de serotonina per ceruloplasmina. Isoniazido, del altere latere, pare inhibir solmente le secunde del duo mentionate itinerarios.

4. Es etiam discutite le possibile signification de iste constatationes con respecto a un conception de fibrosis.

SUMMARIO IN INTERLINGUA

(See page 207 for original article)

Le Effecto Hypnotic de un Nove Propanediol Dicarbamate, W583 (Un Studio Duple-Cec a Dosage Simple e Duple)

W 583 es un nove derivato del serie de propanediol dicarbamate. Le effecto sedative hypnotic del droga esseva evalutate in un studio a dosage simple e duplate sub conditiones duple-cec, con le reactiones subjective del patientes usate como mesura del responsa therapeutic. Esseva trovate que le droga es un salve agente hypnotico-sedative. Su effecto esseva significativemente superior al placebo e characterisate per un plus profunde e plus longe somnio. Le effecto esseva retardate per inter 1 e 6 horas, possibilemente in consequentia del modo de absorption. Le droga esseva remarcabilemente libere de toxic effectos lateral in nostre studio que esseva un studio a breve vista. Evalutationes additional del proprietates sedative e hypnotic del droga sub conditiones clinic es recommendate.

THE HYPNOTIC EFFECT OF A NEW PROPANEDIOL DICARBAMATE, W 583 (A DOUBLE BLIND, DOUBLE DOSE STUDY)*

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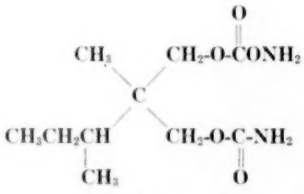
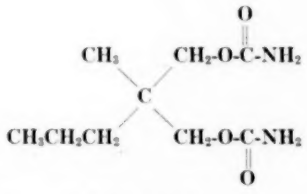
W 583 is a new compound of the propanediol series which differs from meprobamate in having more pronounced hypnotic activity. It is 2-methyl-2-sec-butyl-1,3-propanediol dicarbamate. Its structure is shown below, and compared to Meprobamate.



W 583



Meprobamate

The drug had been found to be nontoxic, except for minimal respiratory depression in animals (Berger[1]). Due to these properties, it was of interest to investigate the hypnotic effect of the drug in humans.

Case Material and Methods. Twenty-five patients were selected in the outpatient clinic of Hahnemann Hospital. They were all suffering from various medical disorders and associated night restlessness and insomnia. The average age of 18 patients who were available for follow-up was 40 and ranged from 16 to 74; there were 3 males and 15 females. The drug was supplied in identical capsules coded as WM-1, WM-2, WM-3, and WM-4. The four drugs were given sequentially at bedtime, each being given for one week or more, until clinical effectiveness could be established. It was known that two of the coded capsules contained placebo, while one contained 200 mg. and one 400 mg. of W 583. On completion of the period of 4 weeks or longer, the patients were shifted to a known combination of 50 mg. pentobarbital and 200 mg. W 583 for a period of one or more weeks. The hypnotic effect was evaluated clinically by the time of onset, depth, and duration of the patient's sleep, as obtained by weekly interview of the patients. Identical questions were asked each patient at each

*This study was supported in part by a grant from Wallace Laboratories.

TABLE 1.—RESULTS OF DOUBLE BLIND STUDY

Serial No.	Initials Age, Sex and Race	Diagnosis	Response* 50 mg. pentobarbital and 20 mg. W 583	WM-1 (200 mg. W 583)	WM-2 (Placebo)	WM-3 (400 mg. W 583)	WM-4 (Placebo)	Side Effects and Remarks
1.	A. T. 30, F, N.	Anxiety reaction; obesity	4	2	2	3	2	
2.	H. B. 50, F, W.	Conversion reaction.		1	1			
3.	B. McK. 55, F, N.	Anxiety reaction.				4 4	0	'Wonderful sleep' 'Best sleeping pill she ever had.'
4.	T. L. H. 29, M, N.	Reaction to stress.		2	2			
5.	B. R. 16, F, N.	Asthma; pruritus.	3	2	0	3	1	Bad taste in mouth. Dryness of mouth.
			4	–	–	4†	3	Drowsy in A.M.—† Slept the whole night
						3†	1	through, not drowsy. †
6.	M. N. 35, M, W.	Conversion reaction. Globus hystericus.	3	1	2	3†	1	Effect in 4 hours. † All tablets b.i.d.
7.	A. G. 47, F, N.	Conversion reaction. Pruritus, psychogenic.	4 and +	2	0	4†	3	† 400 mg. W 583 made patient "dopey" and dizzy; could not wake up; slept a long time.
8.	G. N. 59, F, N.	Conversion reaction.	4 4	2	0	3	0	
9.	G. C. 56, F, N.	Psychophysiologic reaction-cardiovascular.		1 1	0			Found Combid superior to 200 mg. W 583 b.i.d.
10.	M. D. 57, F, W.	Bronchial asthma. Anxiety reaction.	–	–	–	4 4	0	Onset of sleep in 1 hour; slept all night through. Could not do this before.
11.	S. R. 15, F, N.	Reaction of adolescence.	3 4	2	1 0	3†	0	Took 200 mg. and 400 mg. W 583 b.i.d.† One

11.	S. R. 15, F, N.	Reaction of adolescence.	3 4	2	1 0	3†	0	Took 200 mg. and 400 mg. W 583 b.i.d.† One tablet at bedtime; the patient was awake for several hours after taking the pill; onset of sleep in 1 hour after pentobarbital and W 583 preparation. Occasionally, sleepy after the latter in the morning.
12.	M. P. 18, F, N.	Conversion reaction. Hyperthyroidism (?).		0	0			
13.	R. T. 26, M, N.	Conversion reaction.		2	0			
14.	A. P. 43, F, N.	Anxiety reaction.	4	1	2	3 2 3 2	1 0 0	Definite hypnotic effect of 400 mg. W 583; groggy sensation when awakened at night. Amytal, gr. iii found to be more effective than 400 mg. W 583. Sleepy next day with Amytal.
15.	E. D. 41, F, N.	Conversion reaction	3†	2	0 0	2	2	†—Felt her face numbed after pentobarbital and W 583 preparation.
16.	A. W. 30, F, N.	Anxiety reaction.	2	0	0	2	0	Transiently drowsy.
17.	N. K. 74, F, W.	Reaction of late life.		2				Palpitation. Felt "dopey" on 200 mg. W 583. Stopped pills.
18.	C. T. 37, F, N.	Pruritus; neurodermatitis. Conversion reaction.	4	0	0	3	2	

*Key to grading of response: 0 = No response.
1 = Slight hypnotic effect.
2 = Moderate hypnotic effect.
3 = Good hypnotic effect.
4 = Marked hypnotic effect.

Note: Each grading relates to a period of one week.

†This symbol shows the treatment period for each patient during which the side effect at right occurred.

visit in order to eliminate the influence of the examiner. The hypnotic effect was graded as follows: 0 = no effect; 1+ = slight; 2+ = moderate; 3+ = good; 4+ = marked effect. Careful observations and inquiries about possible side effects were undertaken and laboratory studies (leukocyte count, differential, urinalysis, and liver function tests), were performed once or more during the study.

Results. Eighteen of 25 patients given the drug, returned to the clinic for follow-up. The patient data and the numerically related results are shown in Table 1. Ten of these 18 patients completed the 5 weeks or longer study, and a total of 82 patient weeks of therapy were observed. Of the 15 patients taking 200 mg. W 583, 7 patients found it definitely more effective than placebo, 6 found no difference, and 2 patients thought the placebo more effective. The 400-mg. dose of W 583 had definite hypnotic effect; 11 out of 12 slept better and longer, without waking up. One patient (case 16) claimed to have been just as drowsy after placebo and the 200 mg. dose, as after 400 mg. of W 583, which tends to invalidate her observations. The onset of hypnotic effect was reported as varying from 1 to 6 hours after oral administration, possibly related to varied rates of absorption. With one exception, no early morning "hangover" was reported after either the 200- or 400-mg. doses. This one patient (case 18), with neurodermatitis, felt that the 400-mg. capsules were too strong, and was alarmed by the depth of sleep.

The mean response (1+, 2+, 3+, 4+) for each of the groups was determined, as well as the standard deviations of the group and of the mean of each group (Table 2). Of the unknown drugs, WM-3 showed the best response, 3.11, and WM-1 was next with 1.35. The statistical significance of the response is shown in Table 3. WM-3, which later was found to contain 400 mg. of W 583, was shown to be significantly superior ($p<0.001$) to the other 3 unknowns and in the same range ($p = 0.09$) of usefulness as the known combination of agents. WM-1 was found to be significantly superior to WM-2 ($p<0.01$) but not to WM-4 ($p = 0.23$). Therefore prior to receiving the code the activity of the four unknowns was proven to be as follows: WM-3>WM-1>WM-2 = WM-4. The code confirmed that WM-3 contained 400 mg. of W 583; WM-1 contained 200 mg. of W 583; and that WM-2 and WM-4 were placebos.

Two patients (cases 6 and 11) were taking 200 mg. and 400 mg. of W 583 twice daily with good results. Apart from the patient (case 7), who experienced drowsiness from 400 mg., there were no remarkable side effects observed. One patient (case 5) has complained of a bad taste and dryness in the mouth, but this is not definitely related to the effect of W 583. It is of interest that one patient (case 16) has been drowsy on placebo, on the drug, and on the combination of 50 mg. pentobarbital and 200 mg. W 583. Of the 11 patients taking this combination, 8 had marked hypnotic effect and 3 had good sleep. Three patients (cases 5, 6 and 16) in this group reported better sleep with 400 mg. W 583 than with the pentobarbital combination, but objective questioning failed to confirm this. There was little doubt in most patients as to the drug or the pentobarbital combination being superior (to the placebo). One patient (case 11) on the combined drugs has experienced an early morning sleepy feeling after awakening. When the effect of the agent seemed doubtful, the agents were given for additional weekly periods (cases 5, 8, 10, 11, 14, and 15).

Routine blood counts, urinanalysis and occasional liver function tests were normal in all instances. The longest

continuous period on 400 mg. was 3 weeks in one patient (case 14). However, most patients had the drug for 1 to 2 weekly periods. The drug in this group of patients appeared to be remarkably free of side effects and toxic effects. One patient (case 9) who also used the drug as a daytime sedative (200 mg. W 583 twice daily) found it less effective than Combid, taken previously by him. One patient (case 14) who had severe insomnia has also received Amytal 200 mg. She had more markedly deep sleep on Amytal than on either 400 mg. W 583 or the barbiturate combination, but she was sleepy the following day. The same patient used to be awakened at 2 A.M. by her returning husband, and on 400 mg. W 583 she felt "groggy" at 2 or 3 A.M., supporting the hypnotic effect of W 583. These instances are not meant as a comparative study, as they are isolated examples.

TABLE 2.—MEAN GROUP RESPONSE

Group	*Weeks Treated*	*Mean Response*	*Standard Deviation of Group*	*Standard Deviation of Mean*
WM-1 (200 mg. 583)	17	1.35	±0.77	±0.187
WM-2 (Placebo)	17	0.59	±0.84	±0.204
WM-3 (400 mg. 583)	19	3.11	±0.70	±0.161
WM-4 (Placebo)	16	1.00	±1.06	±0.265
200 mg. 583 + 50 mg. pentobarbital	13	3.54	±0.70	±0.193

TABLE 3.—STATISTICAL SUMMARY OF PATIENT RESPONSE TO W 583 AND PLACEBO

Group	*WM-2 (Placebo)*	*WM-3 (400 mg. 583)*	*WM-4 (Placebo)*	*200 mg. 583 + 50 mg. Pentobarbital*
WM-1 (200 mg. 583)	p*<0.01	p<0.001	p=0.27	p<0.001
WM-2 (Placebo)	—	p<0.001	p=0.23	p<0.001
WM-3 (400 mg. 583)	—	—	p<0.001	p=0.09
WM-4 (Placebo)	—	—	—	p<0.001

*p is the probability that the mean group difference was a chance occurrence.

Discussion. W 583 appeared to have marked hypnotic properties, but without the respiratory depressant effects observed in animals. In animals, it is similar to meprobamate in length of action, anticonvulsant properties and degree of toxicity (Wallace Laboratories[4]). Preliminary studies in humans have shown it to have sedative and hypnotic value. Occasional headaches

the next day, dizziness or unsteadiness were found equally after W 583 and placebo (Wallace Laboratories[4]).

In our double blind study, W 583 was found to have definite hypnotic effect. Even with low doses (200 mg.), the effect was mild but distinct. "Hypnotic effect" of placebo was occasionally reported by some psychoneurotic individuals. Excluding those patients who reported sleeping as well with placebo as with the drug (200 mg.), about two-thirds of the patients had better sleep on the drug, and one-third on placebo, a frequent finding in subjective response studies. Doubling the dose brought out a highly significant hypnotic effect of this new dicarbamated propanediol derivative. With one exception, all patients slept better after taking the drug. On this dose the patients noted the difference within the first 2 days, pointing out the aphorism that a double blind study (when pharmacologically active doses are given) is an experiment in which everybody but the doctor knows what is being given (Gerard[3]).

In several patients placebo seemed to be more potent during the first week following active drug administration; however, the subsequent one or 2-week periods eliminated this "overlap" effect.

The potentiation of pentobarbital and W 583 was anticipated, because meprobamate in large doses synergistically prolongs hexabarbital anesthesia in animals. This is not observed with meprobamate when given in low doses (Berger[2]). A more marked synergistic action between pentobarbital and W 583 in moderate doses is probably inherent in the more pronounced hypnotic action of the latter compound. The sedative-hypnotic property of W 583 was useful in several restless patients when it was taken during the day. Perhaps this drug could be of value in those restless patients who are in danger of barbiturate addiction.

The slow onset of action with W 583 makes this drug suitable for those who are able to fall asleep initially but who wake up later during the night. Combination with a rapidly acting hypnotic would be advantageous in cases where the difficulty lies in the induction of sleep. The remarkable lack of toxicity of W 583 suggests the need for further clinical studies of the potential usefulness of this agent. Side effects were few; these were related to some occasional drowsiness and dryness of the throat. Dizziness, unsteadiness or headaches the following day were not reported by or observed in our patients.

Summary. W 583 is a new derivative of the dicarbamated propanediol series. The hypnotic sedative effect of the drug was evaluated in a double-dose, double-blind study, using the patient's subjective reaction as a measure of the therapeutic response. The drug was found to be a safe hypnotic-sedative agent. Its effect was significantly superior to placebo, and characterized by deeper and longer sleep. There was a 1- to 6-hour delay in the onset of effect, possibly due to the absorption pattern. The drug was remarkably free of side effects and toxic effects in our short term study. Further clinical evaluation of the sedative and hypnotic properties of this drug is recommended.

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(Interlingua on page 206)

AMELIORATION OF HUMAN HYPOGLYCEMIC SYMPTOMS BY INTRAVENOUS FRUCTOSE

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In addition to being the only sugar normally circulating in significant amount, glucose is also the only fuel the brain can directly metabolize (Himwich[5]). Teleologically, therefore, rapid depression of blood sugar evokes prompt adrenomedullary discharge of epinephrine to combat hypoglycemia by enhancing hepatic glycogenolysis (Himwich[6]). The patient experiences resultant hyper-epinephrinemia as lightheadedness, hunger, inward trembling, sweating, tachycardia, weakness and diplopia. If severe hypoglycemia persists despite increased outpouring of glucose from the liver, progressive depression of cerebral metabolism is marked by headache, mental confusion, stupor, coma and convulsions (Himwich[7]).

The above manifestations have long been specifically attributed to deficiency of glucose, because they appeared only when circulating glucose was low and were abolished only by raising its blood level (Bollman and Mann[1]). It is now known, however, that brain tissue can phosphorylate fructose, another hexose, when glucose is absent from the incubating medium (Slein, Cori and Cori[19]). Since fructose is often used in conjunction with high insulin dosage during early treatment of diabetic ketosis, the possibility warranted investigation that hyper-fructosemia might prevent or mollify the epinephrine response to profound hypo-glucosemia. It was found that symptoms induced during intravenous insulin tolerance tests were much milder when subjects were concomitantly receiving infusions of fructose. On the other hand, if intravenous fructose was withheld until hypoglycemic manifestations developed, its administration was then incapable of arresting symptoms promptly.

Materials and Methods. The subjects were healthy young adults, 6 men and one woman. All were consuming normal diets prior to testing, and all tests were done at bed rest in the fasting state. Baseline intravenous insulin tolerance tests were first performed, using 0.1 unit of regular insulin per kg. of body weight

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TABLE 1.—BASELINE INSULIN TOLERANCE TESTS

Subject	Insulin dose (unit/kg.)	Fasting blood glucose (mg./100 ml.)	Lowest blood glucose		Hypoglycemic symptoms			Eosinopenia at 4 hours (% fall)
			(mg./100 ml.)	Min. after insulin	Time of onset (min.)	Duration (min.)	Severity	
H.S.	0.1	95	20	20	20	35	+++*	83
E.K.	0.1	94	21	20	19	25	+++	42
R.H.	0.1	82	14	20	17	25	+++	88
M.U.	0.1	85	17	20	27	14	++	79
J.G.	0.1	100	27	30	27	33	++	73
R.M.	0.25	94	13	30	30	45	++	87
C.G.	0.1	83	29	30	39	15	+†	81
Mean		90	20	24	26	27		76
S.E.M.		±3	±2	±2	±3	±4		±6

*Intense malaise, hunger, sweating, inward trembling, weakness. No loss of consciousness.
†Slight lightheadedness, extreme hunger.

TABLE 2.—INSULIN TOLERANCE TESTS DURING FRUCTOSE INFUSION

Subject	Insulin dose (unit/kg.)	Blood fructose* (mg./100 ml.)	Blood glucose when insulin injected (mg./100 ml.)	Lowest blood glucose		Hypoglycemic symptoms			Eosinopenia at 3 hours (% fall)
				mg./100 ml.	Min. after insulin	Time of onset (min.)	Duration (min.)	Severity	
H.S.	0.125	80	90	15	30	23	17	+−++	51
E.K.	0.1	86	111	20	30	0	0	0	16
R.H.	0.1	113	55	25	30	47	10	+	58
M.U.	0.15	95	86	20	45	45	8	0−+	58
J.G.	0.2	140	74	28	60	55	21	+	37
R.M.	0.25	145	111	16	45	45	4	0−+	42
C.G.	0.25	166	88	31	60	0	0	0	−18†
Mean		118	88	22	43	43	9		35
S.E.M.		±12	±7	±2	±5	±5	±3		±10
"p"‡			<0.9	<0.4	<0.001	<0.005	<0.001		<0.005

*Mean fructose concentration from time insulin given at 30 minutes until end of infusion at 90 minutes.
†Total eosinophil count exceeded fasting value.
‡Significance of change from corresponding mean value during baseline insulin tolerance test.

in 6 subjects and 0.25 unit per kg. in the seventh (Table 1). On another day, fructose* was administered intravenously for 90 minutes at a rate of 1.5 gm. per kg. per hour. The second intravenous insulin tolerance test was started after fructose had been infused for 30 minutes. The range of insulin dosage was the same, but 4 subjects received a larger amount than during the baseline test (Table 2).

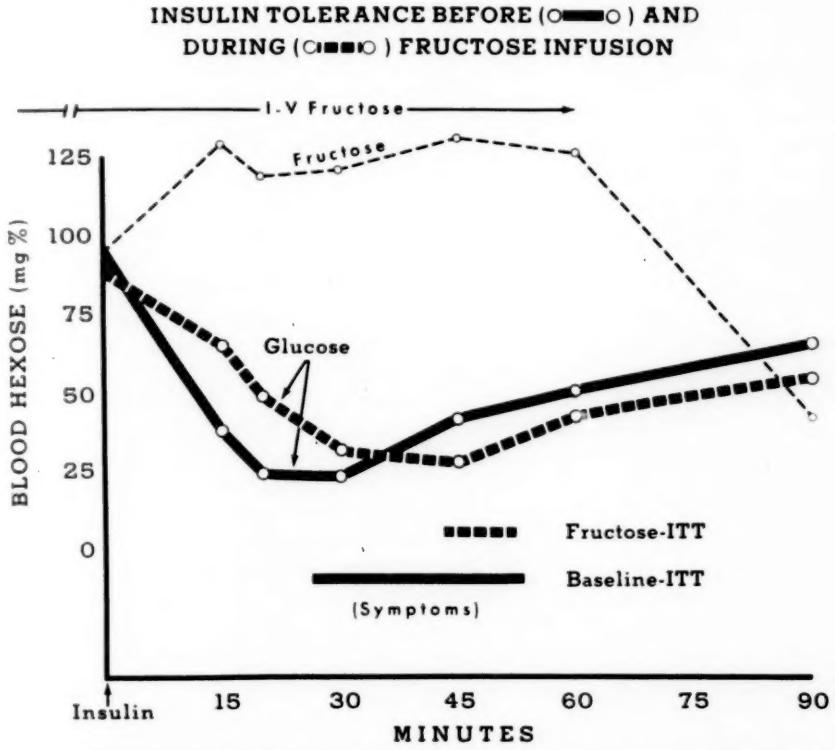

Fig. 1.—Mean values for the 7 subjects are shown. During the baseline test blood glucose fell faster, and severe hypoglycemia (below 30 mg. per 100 ml.) lasted longer, than during the fructose-insulin tolerance test. Both duration and intensity of symptoms were greater during baseline test.

On 2 different days, one individual was given 0.1 unit of regular insulin per kg. intravenously. When definite symptoms of hypoglycemia supervened, he received by vein 50 ml. of 50% glucose or fructose, respectively.

During both insulin tolerance tests samples of venous blood were obtained just before injecting insulin, and thereafter at 15, 20, 30, 45, 60 and 90 minutes. On specimens of oxalated whole blood containing potassium fluoride to inhibit glycolysis, total blood sugar was determined in duplicate by the Somogyi-Nelson method (Nelson[12]), and fructose in duplicate by the method of Roe[16]. Blood glucose was obtained by subtracting the fructose value from the total blood sugar level. Since all glucose concentrations were normal or subnormal, correction of fructose values was not necessary (Miller *et al.*[11]). Total eosinophil counts were done in triplicate on all blood samples, using the Randolph technique[14].

Results. During baseline insulin tolerance tests (Table 1 and Fig. 1) blood glucose fell rapidly and profoundly, lowest values occurring 20 or 30 min-

*Solutions of fructose were generously supplied by Mead Johnson and Company, Evansville, Indiana.

utes after insulin. Six subjects reported initial symptoms between 17 and 30 minutes after receiving insulin, and noted progressive appearance of lightheadedness, inward trembling, sweating, tachycardia, weakness, hunger, and irritability. Significant symptoms lasted from 14 to 45 minutes (mean of 27 minutes for the entire group), and they continued to be variably weak, irritable and hungry until they ate after completing the test. The seventh subject (C.G.) experienced only slight lightheadedness and extreme hunger.

When insulin tolerance tests were repeated during fructose infusions, using the same or increased dosage of insulin (Table 2), comparably low blood glucose values were reached in all but one subject (R.H.). However, the rate of glucose disappearance was slower and the duration of maximal hypoglycemia was shorter (Fig. 1). The lowest blood glucose value occurred 30 minutes after insulin administration in 3 subjects, 45 minutes after insulin administration in 3 subjects, 45 minutes after insulin in 2 of them, and 60 minutes after insulin in 2 others. Two subjects had no symptoms, one had significant but quantitatively decreased complaints, and the other 5 had only minimal and short-lived discomfort. Symptoms lasted from 0 to 21 minutes, averaging 9 minutes.

A single demonstration, in subject H.S., confirmed the great superiority of glucose over fructose in abolishing hypoglycemic symptoms elicited by 0.1 unit of regular insulin per kg. Severe manifestations subsided almost completely one minute after the intravenous administration of 50 ml. of 50% glucose, and disappeared entirely within 8 minutes. In a matching experiment, infusion of 50 ml. of 50% fructose was wholly ineffective in modifying either the severity or duration of similar symptoms. On another day, the same individual was given 0.13 unit of regular insulin per kg., and subject E.K. received 0.12 unit per kg. Twenty-five minutes later, when hypoglycemic complaints were maximal at glucose levels of 8 mg. and 6 mg. per 100 ml. respectively, 50 ml. of 50% fructose were administered to each man. Neither subject noted any amelioration of symptoms. Five minutes after the fructose injection, 50 ml. of 50% glucose were infused into E.K., and within one minute he reported marked, but not complete, subsidence of symptoms. Incapacitating manifestations meanwhile persisted for 45 minutes in H.S., who was not given glucose

Circulating eosinophils showed different patterns of response to the 2 insulin tolerance tests (Fig. 2). During baseline tests the eosinophil count rose sharply as symptoms developed, the mean peak being 36% above control value 45 minutes after insulin was given. It then declined progressively to a mean low point 76% below initial value (range of fall was 42% to 88%) four hours after insulin injection (Table 1). In contrast, during fructose-insulin tolerance tests mean eosinophil count increased only 9% above control value at 45 minutes; and maximal eosinopenia not only averaged 35% (range of minus 18% to 58%), but occurred an hour earlier (Table 2).

Discussion. Tagnon and Corvilain[21] recently reported even more striking amelioration of hypoglycemic symptoms by fructose than was observed in the present study. Using 0.1 unit of insulin per kg. in both control and fructose-insulin tolerance tests, they started the fructose infusion (90 gm. in 60 minutes) simultaneously with insulin injection into 12 subjects who had registered typical complaints during the control test. All subjects remained entirely symptom-free, despite minimal glucose values reported as

"0 mg. per 100 ml." (!) in 2 subjects, and less than 10 mg. per 100 ml. in 4 others. The curves showing blood glucose fall and rebound were superimposable, the mean lowest value occurring at 25 minutes in both tests.

Blunting of symptomatic hypoglucosemia by concomitant hyperfructosemia could occur via one or more of 3 mechanisms: (1) direct cerebral utilization of fructose, its metabolic fragments, or a non-carbohydrate substrate; (2) direct assimilation of fructose by muscle or other non-hepatic peripheral tissue, thereby sparing available glucose for the brain's energy needs; or (3) hepatic gluconeogenesis from fructose, resulting in enhanced release of glucose into the hepatic vein.

Tagnon and Corvilain[21] concluded that their remarkable findings represented the clinical counterpart of the demonstration by Slein, Cori and Cori that rat brain avidly phosphorylates fructose in the complete absence of glucose[19]. However, direct measurement of cerebral uptake of fructose, pyruvate and lactate in man has shown that utilization of all 3 substrates is zero under both normoglycemic and severely hypoglycemic conditions (Seltzer, Eisenberg and Sensenbach[18]). Cerebral extraction of non-carbohydrate intermediates, such as ketone bodies, is also negligible under all circumstances (Himwich[8]).

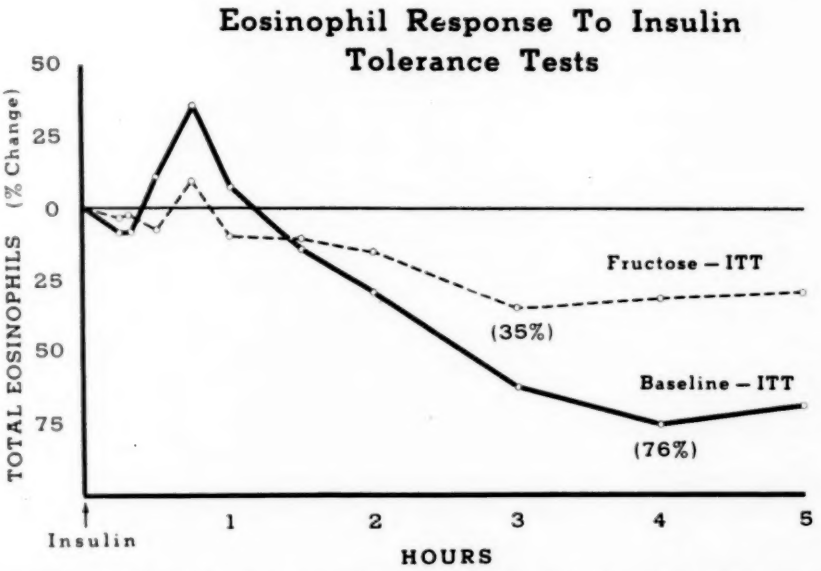

Fig. 2.—The mean curve showing eosinophil changes during and after the baseline test, with sharp initial rise and deep secondary fall to a low point at 4 hours, resembled that induced in normal subjects by 1.0 mg. of epinephrine intramuscularly (Samuels[17]). Eosinophilic variations during the fructose-insulin tolerance test were qualitatively similar but greatly muted in amplitude, suggesting a weaker adreno-medullary response to hypoglycemia.

The intensity and duration of hypoglycemic symptoms depend not only upon the actual depth of blood sugar depression, but also upon its speed of fall and the duration of the hypoglycemic period. In the present study, the milder manifestations at comparably

low blood glucose levels during the fructose-insulin test were probably related to the slower rate of fall and the shorter interval of profound hypoglycemia (glucose values below 30 mg. per 100 ml.). The latter findings in turn signified that more glucose was available for cerebral use, either because of decreased peripheral uptake or increased hepatic production.

Although animal studies using C^{14}-labeled fructose show the liver alone to be capable of oxidizing fructose directly (Chernick and Chaikoff[2], Wick, Sherrill and Drury[26]), other research groups (Miller *et al.*[10], Van Itallie *et al.*[23], Weichselbaum, Margraf and Elman[24], Weinstein and Roe[25]) have interpreted wide arteriovenous differences for fructose as indicating its assimilation by human peripheral tissue. Similarly, one of the present authors has found A–V differences up to 20 mg. per 100 ml. across the arm during fructose infusions lasting 90 minutes (Seltzer, Eisenberg and Sensenbach[18]); in addition, average fructose extraction was the same at both normal and very low blood glucose levels. Fructose may thus play part of its protective role by acting as a substitute carbohydrate in muscle and skin, thereby shunting circulating glucose to the cerebral locus where it is uniquely required.

Notwithstanding the preceding observations, most experimental evidence indicates that fructose primarily blunts the impact of hypoglycemia on the brain by serving as a precursor of glucose. Bollman and Mann[1] concluded from their classical studies in hepatectomized and eviscerated dogs that fructose was utilized directly only in the liver and intestinal tract, where conversion to glucose accounted entirely for its efficacy in alleviating hypoglycemia. Hepatic vein catheterization of normal subjects subsequently showed that increased production of glucose was proportional to the rate of fructose infusion (Weichselbaum, Margraf and Elman[24]); although, quantitatively, less than 10% of administered fructose was actually converted to glucose by liver. This low turnover ratio accounts for the limited effectiveness of fructose in attenuating hypoglycemic symptoms, and explains why both experimentally (Bollman and Mann[1], Corley[3], Herring, Irvine and MacLeod[4], Mann and Magath[9], Noble and MacLeod[13]) and clinically it is unable to reverse already-existent manifestations of low blood sugar.

Two observations in the present study support the idea that intravenous fructose is essentially equivalent to a much smaller injection of glucose. First, in each subject the lowest glucose value during the fructose-insulin tolerance test occurred later than during the baseline test (Tables 1 and 2). Secondly, during the fructose-insulin test 4 subjects required more insulin to produce comparably low blood glucose levels, and one individual given the same dosage both times (R.H.) showed less depression of glucose during the fructose infusion. Since fructose utilization does not require insulin (Smith, Ettinger and Seligson[20]), this seemingly diminished insulin activity must have resulted from simultaneous replenishment of blood glucose even as its rate of removal was being accelerated by the injected insulin.

It bears strong emphasis that, although the protective effect of fructose against hypoglycemia is a real phenomenon, it is quantitatively minor and has no clinical application. Because of the low turnover rate of fructose to glucose in liver, it can only be demonstrated when insulin dosage is small. Specifically, therefore, infusion of fructose in conjunction with large amounts of insulin during initial treatment of dia-

betic ketosis does not constitute a reliable buffer against hypoglycemia. Once insulin resistance is overcome, and a flood of insulin activity inundates the patient, the limited antihypoglycemic effect of fructose will shortly be obliterated. Intravenous glucose should therefore be substituted for fructose when total blood sugar starts to fall*.

Finally, the eosinophil responses set off by the 2 tolerance tests confirmed that respective intensity of symptoms was directly due to the magnitude of epinephrine release. During baseline testing, the 35% rise of eosinophils coincident with development of complaints represented the "Phase I" response to epinephrine reported by Samuels[17]. He found a mean 47% increase of eosinophils 17 minutes after giving 1.0 ml. of 1:1000 epinephrine hydrochloride intramuscularly, and suggested that this eosinophilia involved more complex mechanisms than the accepted one of simple splenic contraction. Subsequent disappearance of eosinophils during the next 4 hours illustrated the well-known eosinopenic response to epinephrine (Recant *et al.*[15]). During the fructose-insulin tolerance test, however, absence of an important early rise, and of significant eosinopenia 3 or 4 hours later, implied that compensatory epinephrine release was minimal. This conclusion fitted well with the very mild symptoms noted by 6 of the 7 subjects. It is interesting that, having observed similar obtunding of insulin-induced eosinopenia during fructose administration, Tagnon, Corvilain and Scohy[22] erroneously interpreted it to mean that the hypothalamus is able to utilize fructose directly. Clinically significant cerebral uptake of any substrate but glucose, under any circumstances, awaits unchallengeable demonstration.

Summary and Conclusions. Intravenous insulin tolerance tests were performed twice in 7 normal subjects, the second test being done during intravenous administration of fructose. Although lowest glucose values were comparable, hypoglycemic symptoms were markedly attenuated in the presence of high blood concentrations of fructose. Symptoms persisted without abatement, however, if administration of fructose was delayed until onset of symptoms.

The partially protective effect of fructose is mediated principally via hepatic gluconeogenesis and subsequent replenishment of circulating glucose. Direct peripheral utilization of fructose, permitting shunting of glucose to brain, appears to play a subsidiary role in combatting cerebral hypoglycemia.

Since only a small fraction of infused fructose is converted to glucose, its buffering effect against hypoglycemia is clinically insignificant. Fructose, therefore, offers no protection against hypoglycemic hazards attending the therapeutic use of insulin.

*Values for blood sugar by the Folin-Wu and Somogyi-Nelson copper-reduction methods represent total blood hexose, that is, the sum of glucose and fructose concentrations. Enzymatic methods using glucose oxidase, for example, "Glucostat," are specific for glucose.

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SUMMARIO IN INTERLINGUA

Melioration de Symptomas Hypoglycemic in Humanos per Fructosa Intravenose

Tests de tolerantia pro insulina intravenose esseva effectuate duo vices in 7 subjectos normal, le secunde vice durante le administration intravenose de fructosa. Ben que le plus basse concentrationes de glucosa esseva comparabile in le duo situationes, le symptomas de hypoglycemia esseva marcatemente attenuate in le presentia de alte concentrationes de fructosa in le sanguine. Le symptomas persisteva sin attenuation, si le administration de fructosa esseva retardate usque al declaration del symptomas.

Le effecto partialmente protectori que es exercite per le fructosa es mediate principalmente via un gluconeogenese del hepate, con subsequente re-approvisionamento de glucosa in le circulation. Le directe utilisation peripheric de fructose, permittente le transferimento de glucosa al cerebro, pare haber un rolo subsidiari in combatter le hypoglycemia cerebral.

Viste que solmente un micre fraction del infundite fructosa es convertite in glucosa, su effecto protectori contra hypoglycemia es clinicamente insignificative. Le conclusion es que fructosa non representa un protection contra le hasardos de hypoglycemia que accompania le uso therapeutic de insulina.

PROGRESS
OF
MEDICAL SCIENCE

OPHTHALMOLOGY

UNDER THE CHARGE OF

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THE PATHOGENESIS OF PAPILLEDEMA IN INTRACRANIAL DISEASE: A REVIEW OF THE LITERATURE

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PRECISELY one hundred years ago von Graefe[30] published his classic paper "Complication of optic neuritis with cerebral disease" in which he stated: "Although there were no signs which could show a direct relation (of edema of the optic disc and venous engorgement) to the intracranial tumor, it seemed reasonable to me to look for a common relation between both, after I had observed four times a coincidence between the above mentioned optic neuritis and sarcomatous brain tumors. . . . I came to the conclusion that the relationship would be only a secondary one, and would be caused by the pressure of such tumors on the cavernous sinus. Naturally, such pressure first causes hyperemia of the retinal veins which is demonstrated by enlargement and tortuosity of the veins. . . . If this connection with mechanical hyperemia is correct, it should be found in a similar way not only with brain tumors but also in other causes of increased pressure on the basis cranii and within the orbit."

A few years later Sesemann[23] demonstrated anastomoses of the ophthalmic and facial veins which weakened the hypothesis that pressure on the cavernous sinus resulted in congestion of the retinal veins and edema of the optic disc. Otherwise, von Graefe's observations as to the association of increased intracranial or orbital pressure and papillary venous congestion in the pathogenesis of papilledema remain quite valid. His prediction that other causes of increased intracranial and orbital pressure would be found to result in papilledema has proved correct.

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The list of such causes now includes brain abscess, subdural hematoma and hydroma, thrombosis of the dural sinuses, congenital deformities of the skull, hydrocephalus, Guillain-Barré syndrome, spinal cord tumors, poliomyelitis, benign intracranial hypertension and hypoparathyroidism. The list of orbital causes includes, in addition to various orbital tumors, malignant exophthalmos, Paget's disease, and congenital deformities.

Though von Graefe[30] correctly pointed to the association between intracranial hypertension and venous congestion of the optic disc, the precise mechanism by which one leads to the other remained obscure. Even today, our knowledge is not much more specific. It is, therefore, the purpose of this paper to review some of the more recent clinical and experimental observations which may have some bearing on this problem.

Duke-Elder[7] in his recent revision of Parsons' "Diseases of the Eye" gives a concise summary of present concepts of the pathogenesis of papilledema: "Since the optic nerve is enclosed up to the lamina cribosa within meningeal sheaths common to the brain, and since the subarachnoid and subdural spaces around the nerve are freely continuous with those around the brain, any rise in the intracranial pressure becomes equally evident around the nerve as within the cranium. When this occurs the subarachnoid space may sometimes become so distended that it is ampulliform just behind the globe.

"As a result, oedema develops at the optic disc; this is a purely hydrostatic, non-inflammatory phenomenon. Its cause has been in dispute. The oedema has been ascribed to the propulsion of cerebrospinal fluid through the lamina, to the imbibition of fluid by the tissues of the nerve head as occurs around a tumour of the brain, and to other factors; but it is most probable that it is due to compression of the central vessels as they cross the vaginal space, causing collapse of the vein, whilst the thicker-walled artery continues to transmit blood. The central vein is collapsed where it crosses the subdural and subarachnoid spaces. There is often subpial oedema distal to the site of entry of the central vessels into the nerve, but the nerve is normal proximal to this point."

Brégeat[3] in his comprehensive thesis presented to the French Ophthalmological Society in 1956 has analyzed in detail 1244 cases, including 734 cases in which papilledema was observed, from three neurosurgical services in France during the years 1950 to 1955. Many aspects of these cases were tabulated including the presence or absence of papilledema and optic atrophy, associated retinal lesions, associated field defects, visual acuity, course of papilledema, modification of retinal artery pressure, type, size, and location of tumor, rate of progression of papilledema, time of discovery after first neurologic symptom, incidence of papilledema in various age groups, state of ventricles, and presence of herniation. In addition, he presents the most comprehensive review of all aspects of the subject ever undertaken. His statistics in general agree with those of previous investigators regarding the incidence of papilledema with various types and locations of tumors. Papilledema was observed in: 78% of subtentorial tumors; 55% of supratentorial tumors, 86% of cerebellar tumors, 66% of tumors of the cerebello-pontine angle, 65% of frontal tumors, 59% of temporal tumors, 57% of parietal tumors, 69% of occipital tumors, 68% of deep ventricular tumors and 16% of pituitary adenomas and craniopharyngiomas.

In general, the statistics demonstrated in addition that papilledema was more likely to occur with large than with small tumors, with dilatation of the third ventricle than with dilatation of the lateral ventricles or with normal ventricles, and with gliomas than with meningiomas. Among cases of brain tumor in the various age groups, papilledema occurred in descending frequency in the group from age 1 to 5 (81%) to those over 70 years (43.5%) due primarily to the higher incidence of malignant tumors and posterior fossa tumors in the younger age groups.

Valuable though this knowledge is, it does not demonstrate the pathogenesis of papilledema. However, such findings as the extremely high incidence of papilledema in cases with a distended third ventricle and in cases in which herniation was observed should be satisfactorily explained by any hypothesis which is formulated.

On purely theoretical grounds transmission of pressure through the optic nerve sheath, cerebral edema, and venous congestion appear to be important factors. They will be considered in more detail.

TRANSMISSION OF PRESSURE THROUGH THE OPTIC NERVE SHEATH. The passage of cerebrospinal fluid into the optic nerve sheath has received ample confirmation by laboratory studies. The *in vivo* passage of dyes and radio-opaque materials into the normal optic nerve sheath after injection in the cisterna magna has been demonstrated in rats, rabbits, dogs and monkeys by Weed[33], Stuck and Reeves[27], Griffith *et al.*[14], Field and Brierly[9] and Schurr *et al.*[22]. To remove any remaining doubt about the transmission of pressure in full force from the intracranial cavity into the normal optic nerve sheath, recent experiments were performed by Kobiela-Krzystkowa[17] to measure the pressure necessary to cause fluid to flow into the sheath. It was found that from both directions of flow, the pressure was equal and ranged from 150 to 200 mm. water. Thus, the free access of cerebrospinal fluid to the normal optic nerve sheath has been thoroughly established.

However, one possible drawback to considering propulsion of cerebrospinal fluid into the optic nerve sheath as the initiating factor in the production of papilledema is that the optic nerve sheath can be obstructed by intracranial disease processes such as edema, tumor growth, or inflammation.

Walsh[31], however, cites such obstruction as an explanation for the absence of papilledema on the same side as the lesion as in the Foster Kennedy syndrome. He suggests that some unilateral congenital anomaly of the optic nerve sheath may explain the absence of papilledema on the affected side in some cases of brain tumor. He also suggested that bilateral absence of papilledema can be explained by anomalies of the optic nerve sheaths. The demonstration of such anomalies has not been reported in the literature examined.

On the other hand, recent observations[12] on the patency of the optic nerve sheath in monkeys suggest that obstruction of the sheath may occur as a result of slight swelling of the nerve as it passes through the bony canal. It was found that a solution of India ink injected into the cisterna magna with a pressure of 500 mm. of water could be expected to outline the optic nerve sheath within 45 minutes. By this method, obstruction of the optic nerve sheath was demonstrated in one or both optic nerve sheaths of 3 out of 6 monkeys with gradually inflated subdural balloons. Obstruction was present in the sheath of one eye in which papilledema had been observed.

In 2 of the 3 monkeys with sheath blockage the obstruction occurred on the same side as the subdural balloon. In each case, there was no evidence of inflammation of the nerve or the meninges. The obstruction was due apparently to a swelling of such slight dimension as to escape detection by gross or microscopic examination but great enough to prevent passage of India ink under a pressure of 500 mm. of water. No conclusions could be drawn from the small number of experiments except to state that the detection of such obstruction of the sheath of the optic nerve merits additional study.

THE RELATIONSHIP OF PAPILLEDEMA TO CEREBRAL EDEMA. The above experimental observations, if confirmed by further study, may provide support for the theory first proposed by Parinaud[20] in 1879 and supported by Sourdille[25] and others that, in some cases at least, papilledema is a manifestation of cerebral edema. Two cases have been reported recently by Brégeat[3] in which obvious edema was noted throughout the optic nerve fibers from the chiasm to the disc. In each case the findings were present on one side only and the opposite nerve was atrophic. The unilateral edema was effectively demonstrated at necropsy by serial transverse sections of the nerves, the chiasm and the tracts and the surrounding brain structures after careful removal of these structures in one piece and embedding in celloidin. The first case was that of a 62-year-old woman with long standing papilledema with secondary atrophy and visual loss as the result of a posterior fossa cystic angioreticuloma. The second case was that of a 40-year-old man with an encysted intracerebral hematoma and aneurysm on the right side. Optic atrophy was present on the right and papilledema on the left, namely, the Foster Kennedy syndrome. These observations are at variance with previous reports that edema is confined to the anterior portion of the optic nerve. However, for the most part, observations have not been made on the entire length of the nerve, possibly because of the difficulty in obtaining such specimens. Duhamel[5] investigated this point specifically. He found that in 3 cases of early papilledema the edema appeared confined to the disc and nerve fibers just behind the globe, but that in a fourth case in which papilledema was estimated to have been present for at least a month, the edema extended posteriorly to the chiasm. He concluded that papilledema begins at the level of the disc and extends posteriorly. However, he points out the difficulties of interpreting degree of swelling in nerve tissue after fixation and embedding in paraffin. This had been previously emphasized by Wolff and Davies[35] in their experimental study on the pathogenesis of papilledema. It appears, then, that further necropsy study of the entire length of the optic nerve, chiasm, and surrounding brain structures in cases of brain tumor with and without papilledema would be a valuable contribution. Sourdille and Sourdille[26] have urged their neurosurgical colleagues to assist with observations on the following points: 1. The state of the ventricles and particularly the third ventricle in cases of papilledema; 2. The presence or absence of edema of the intracranial portion of the optic nerves in cases of brain tumor of short duration; 3. The presence or absence of marked cerebral edema in the region of the chiasm in cases with high-grade papilledema.

Certain clinical observations are more satisfactorily explained by the theory that papilledema is a manifestation of cerebral edema than by any other theory. One example is the case of frontal tumor or middle ear disease which is cited by Duke-Elder[7] as fre-

quently resulting in a predominence of papilledema on the same side as the lesion. If cerebral edema is the direct cause, one would expect a greater edema in the optic nerve on the same side as the lesion because edema of the brain is usually greater in the hemisphere in which the lesion is located.

A second type of case best explained by this theory is that of the bilateral absence of papilledema in the presence of increased intracranial pressure. Leinfelder[18] reported 9 such cases with cerebrospinal fluid pressure elevated over 200 mm. of water out of 38 cases with brain tumor without papilledema. The usual causes of increased intracranial pressure such as cerebral edema, venous obstruction and ventricular obstruction, do not necessarily result in edema of the chiasm or of the intracranial portion of the optic nerves. In addition, such edema if it should occur might be present for such a short period of time or in such slight degree that it failed to extend to the disc.

Similarly, the presence of papilledema associated with brain tumor in the absence of intracranial hypertension would be explained by involvement of the optic nerve fibers in the edematous process if the edema were relatively localized and if there were no significant venous obstruction or ventricular block to create an increase in intracranial pressure. Leinfelder[18] reported 12 out of 80 cases of brain tumor with papilledema in which the cerebrospinal fluid pressure was less than 200 mm. of water. In 2 of these, a block accounted for the low pressure on lumbar tap. All but one of the remaining 10 cases showed other evidence of increased intracranial pressure such as bulging dura, flattening of the gyri or enlarged ventricles. Walsh[31] points out that the cerebrospinal fluid pressure fluctuates so widely that a single pressure measurement is not necessarily representative of the mean intracranial pressure over a period of time. This might explain the low pressure readings in some of these 10 cases reported by Leinfelder[18]. On the other hand, it is conceivable that in at least a few of these cases cerebral edema leading to flattening of the gyri and bulging of the dura was present only in the region of the tumor, which would be the area visualized at operation, and that a generalized intracranial hypertension involving all compartments of the brain was actually not present.

Still another clinical observation which seems inadequately explained by the usual theory of venous compression by the cerebrospinal fluid in the sheath is that papilledema characteristically takes days or weeks to develop. If compression of the vein by the cerebrospinal fluid in the sheath were the chief factor, papilledema might be expected to result in every case in a matter of minutes or hours after the onset of increased intracranial pressure. Walsh[31] comments "certainly a low-grade papilledema may develop within a few hours but for high grade papilledema several days are usually necessary." Regression of the papilledema usually takes even longer. Such a slow evolution and regression would seem to be more compatible with gradual extension and subsidence of edema throughout the optic nerve fibers.

In general support of this theory, Brégeat[3] stated: "Intracranial hypertension due to cerebral edema, to increased cerebrospinal fluid pressure or to cerebral venous stasis is the most frequent cause of true papilledema. Certainly, mechanical factors are not negligible and we think that in certain cases, an increase in the pressure of the tissue fluid of the optic nerve determines the development of papilledema, but we do not believe that this is the effect of the increased pressure on the central

vein of the retina. When this occurs, there results primarily a retinal edema (thrombosis of the central vein, carotid cavernous fistula). In pure papilledema, on the contrary, due to intracranial hypertension, increased pressure in the central vein is not proven; and the impossibility of making apparent the venous pulse by compressing the globe, shows only in its occurrence, a state of venous engorgement by diminution of the circulatory flow. This venous stasis (which is not a papillary stasis) does not depend directly on a cerebral venous stasis because of the possibility of drainage of the orbital veins; it becomes rather, in certain cases the consequence of local disturbances (perhaps reflexes) created by the appearance of papilledema. The mechanical factor is, therefore, not essential. The state of vasodilatation that one observes in certain regions of the brain could also appear in the optic nerve which is a peduncle of the brain and manifest itself by edema in the place most favorable, which is to say, the papilla. Papilledema appears, thus, to be dependent on cerebral edema of which it is the ophthalmoscopic manifestation. Cerebral edema and papilledema could also depend on the same cause, that is to say, from a disturbance of a common central regulator." Thus, in addition to favoring the importance of cerebral edema over the compression of the central vein, Brégeat[3] suggests the possible role of vasomotor influence in the production of papilledema. He also points out the fact that generalized retinal edema and peripheral retinal hemorrhages are not observed in papilledema, as would be expected if compression of the central vein were the chief factor in the development of papilledema.

THE ROLE OF VENOUS CONGESTION IN THE PATHOGENESIS OF PAPILLEDEMA. Walsh[31] emphasizes the importance of venous congestion in his summary of the pathogenesis of papilledema associated with increased intracranial pressure: "Obstruction to venous outflow is an important factor in the production of papilledema associated with increased intracranial pressure, and such obstruction probably is due to pressure on the central vein where it traverses the perineural space about the optic nerve. Increased intracranial pressure is frequently the factor associated with venous obstruction but decreased intraocular pressure may be associated with it. If obstruction to the venous outflow were the only cause of papilledema we might expect the entire retina to be edematous, but this is not the usual situation encountered. Duke-Elder's suggestion that a colloid chemical factor of unknown nature influences the localization of the edema to the optic disc and its immediate surroundings may be correct." According to Henderson[15], Leinfelder suggested the importance of congestion of the capillary circulation in the disc which is derived from the choroidal artery of Zinn and which therefore is independent of the retinal circulation as an explanation for the localization of edema to the optic disc. Another explanation for this was offered by Wolff and Davies[35] who suggested that the loose structure of the nerve-fiber layer of the disc allows more accumulation of the fluid than does the surrounding retina with its supporting structure of Mullerian fibers. Still another factor has been suggested by van Heuven and Fischer[29] who demonstrated by means of *in vitro* studies that nerve tissue of the disc imbibed fluid more readily than did the retina.

In support of the suggestion regarding congestion of the capillaries of the disc as being a prime factor, it seems more likely that the pressure in the sheath would obstruct the

subpial venules in the region just behind the disc more readily than it would the much larger central vein. This may account for the frequency of hemorrhages on and close to the disc and the infrequency of peripheral retinal hemorrhages in cases of sudden increased intracranial pressure. It should be mentioned that Bedford[1] has demonstrated in dogs and Ryder *et al.*[21] in monkeys that a sudden increase in intracranial pressure does not cause an elevation of the pressure in the dural sinuses. Therefore, the theory that blood is forced from the cavernous sinus causing retinal venous congestion is as unlikely an explanation for the occurrence of retinal hemorrhage in subarachnoid hemorrhage as it is for papilledema. The hemorrhages in the sheath of the optic nerve which have been reported by Walsh and Hedges[32] and by Smith, Kearns and Sayre[24] in cases of subarachnoid hemorrhage can also be explained more satisfactorily by obstruction of the smaller venules of the sheath than by obstruction of the central vein.

With regard to papilledema, obstruction of the smaller vessels behind the disc could be the result of a much more gradual process such as the extension of edema through the nerve as previously suggested. Certainly, factors other than venous congestion must be present to account for papilledema of 6 or 7 diopters because total obstruction of the central vein by itself rarely if ever produces a papilledema greater than 3 diopters.

The relationship of papilledema to increased intracranial pressure has been studied recently in malignant hypertension, and in conditions with increased cerebrospinal fluid protein.

INTRACRANIAL PRESSURE, PAPILLEDEMA AND MALIGNANT HYPERTENSION. An outstanding clinical investigation was reported in 1954 by Taylor, Corcoran and Page[28] in their study "Increased cerebrospinal fluid pressure and papilledema in malignant hypertension." They compared 100 patients with malignant hypertension with 100 hypertensive patients without papilledema. Of those patients without papilledema, 87 had a cerebrospinal fluid pressure of less than 250 mm. of water while 57 of the patients with malignant hypertension had a normal cerebrospinal fluid pressure. A loose correlation between papilledema and increased cerebrospinal fluid pressure was demonstrated; in general, the higher the pressure, the more likely papilledema was. Of those with pressures of over 350 mm. of water, 14 had papilledema and 2 did not. Repeated measurements were made on those patients in whom papilledema was observed to be increasing or decreasing. The height of the pressure had no regular relationship to changes in papilledema in these cases. In general there was no decrease in the Ayala index to indicate the presence of cerebral edema. They concluded that increased cerebrospinal fluid pressure, papilledema and elevated diastolic pressure are more or less independent manifestations of severe hypertensive vascular disease.

Kirby and Hollenhorst[16] reported 2 interesting cases of hypertension in which ligation of the carotid artery was performed on one side because of intracranial aneurysm. Prior to the ligation, the arteriolar changes were similar in the two eyes. Following the ligation, the pressure in the ophthalmic artery as measured with the ophthalmodynamometer was lower on the side of ligation. The retinal arteriolar changes subsequently became much less severe on this same side while progression of the changes occurred in the opposite eye. In one case, exudates and papilledema developed subsequently in the opposite

eye, while the hypertensive changes remained relatively mild on the side of ligation. This fortuitous observation suggests the possibility that papilledema in hypertension can be the result of severe constriction of the vessels in the disc. This, in turn, appears to be due to the increased pressure in the branches of the carotid artery. Such arteriolar narrowing, if severe enough, can undoubtedly disturb the nutrition of the nerve fibers and lead to edema on that basis.

INTRACRANIAL PRESSURE, PAPILLEDEMA AND INCREASED CEREBROSPINAL FLUID PROTEIN. In the past 10 years there have been a number of reports of papilledema associated with an elevated cerebrospinal fluid protein in the Guillain-Barré syndrome, with spinal cord tumors, and following poliomyelitis. Most of these cases, but not all have been associated with increased intracranial pressure. Drew and Magee[4] in 1951 collected 9 cases of Guillain-Barré syndrome with papilledema from the literature and added a tenth case. Feldman, Landau and Halpern[8] collected 4 more cases and added a fifth case of their own. Of these 15 cases, the cerebrospinal fluid pressure was appreciably elevated in 8, not mentioned in 3, normal in 2, one of which had only transient papilledema, and normal in one in which a block was present. The occurrence of papilledema in this syndrome is rare. Drew and Magee[4] suggest that papilledema in these cases may be the result of increased cerebrospinal fluid pressure, or of edema of the brain which has been reported to occur along with edema of the peripheral nerves and spinal roots. They also speculate that the increased cerebrospinal fluid protein interferes with the centripetal flow of fluid from the eye to the brain (postulated by Behr[2]). Two cases of spinal cord tumor with elevated cerebrospinal fluid protein and papilledema were reported by Love, Wagener and Woltman[19]. An internal hydrocephalus was present in each case. The spinal fluid protein was 180 mg. per 100 ml. and 160 mg. per 100 ml., respectively. In a similar case of ependymoma of the cauda equina with papilledema reported by Gardner, Spitler and Whitten[10] the cerebrospinal fluid pressure was 325 mm. of water and the cerebrospinal fluid protein measured 425 mg. per 100 ml. They also reported a case of small acoustic tumor with papilledema in which a communicating hydrocephalus was demonstrated. The protein measured 180 mg. per 100 ml. and the cerebrospinal fluid pressure measured 150 mm. of water.

Weiman, McDowell and Plum[34] collected 8 cases from the literature and added 4 of their own of papilledema following poliomyelitis. The papilledema occurred any time from 11 to 48 days after the onset of the poliomyelitis and lasted from 13 to 140 days. It appeared to be a benign and self-limited condition. The cerebrospinal fluid findings were reported in 4 cases. The matched pressure and protein readings were 147 mg. per 100 ml. with a pressure of 180 mm. of water, 162 mg. per 100 ml. with a pressure of 390 mm. of water, 99 mg. per 100 ml. with a pressure of 140 mm. of water (papilledema developed one week after this tap), and 306 mg. per 100 ml. with a pressure of 600 mm. of water. Gass[11] reported 2 more cases of papilledema following poliomyelitis in which decompression was performed. Cerebral edema was noted at operation. In these cases the cerebrospinal fluid protein was not elevated.

The occurrence of papilledema in these 3 conditions shows some correlation to increased intracranial pressure, but the correlation is not absolute. The importance of the elevated cere-

brospinal fluid protein and of other factors such as cerebral edema must await further study.

Because of the great difficulties encountered in studying this problem by the clinical and pathological approach, many investigators have attempted to produce papilledema in laboratory animals.

THE EXPERIMENTAL PRODUCTION OF PAPILLEDEMA. Such attempts have been reviewed[12] and fall largely into three categories: 1) elevation of cerebrospinal fluid pressure over short periods of time; 2) simulation of intracranial mass lesions and; 3) the production of internal hydrocephalus. In general, it can be said that the methods used have not greatly clarified the pathogenesis, and that a repeatable method for producing a papilledema analagous to that seen in man has not been evolved. In those experiments in which the intracranial pressure was measured, none had lasted longer than 12 hours whereas in man papilledema rarely develops in less than 12 hours after the onset of intracranial disease.

The method of production of papilledema by the gradual inflation of a subdural balloon in the monkey[13] corrects some of these deficiencies and results in a papilledema very similar to that seen in man but the incidence of production of papilledema is low. The monkey appears to be a more satisfactory animal for the study of this problem than does the dog, possibly because of the difference in venous circulation around the optic disc[12,35].

Summary. Von Graefe's[30] original observations as to the association of increased intracranial pressure and papillary venous congestion in the production of papilledema have remained quite valid after 100 years of extensive investigation. The precise relationship between these two factors remains obscure. On theoretical grounds, the transmission of pressure through the optic nerve sheath, the occurrence of cerebral edema and the exact location of the venous stasis seem to be important and are discussed in some detail. The experimental finding of obstruction of the optic nerve sheath due apparently to slight swelling of the intracanalicular portion of the optic nerve is discussed. There is a need for further observations on the patency of the optic nerve sheaths. Brégeat's[3] 2 cases of papilledema in which edema of the entire optic nerve and chiasm on one side was found at necropsy are mentioned. Clinical observations are presented which seem to be explained most satisfactorily by Parinaud's[20] theory that papilledema is a manifestation of cerebral edema.

The relationship of intracranial pressure to papilledema in malignant hypertension and in cases with increased cerebrospinal fluid protein is reviewed. Though there is a close correlation between the height of the pressure and the occurrence of papilledema, the relationship is not an absolute one. The clarification of the modifying factors must await further investigation.

Experimental studies are briefly discussed. A method is needed for producing in a high percentage of experiments papilledema analagous to that seen in man. The monkey would appear to be the most satisfactory animal for this study.

ADDENDUM: Further support to the association between cerebral edema and papilledema is provided by the recent studies of Sahs, A. L., and Joynt, R. L.: Brain Swelling of Unknown Cause. Neurology, **6**, 791, 1956. They biopsied brain tissue in 10 cases of pseudotumor cerebri (all cases of which had bilateral papilledema) and found definite intracellular and extracellular swelling in all specimens. Control specimens obtained from 6 other cases showed no evidence of brain swelling. Prior to this study, cerebral edema had been thought to be present in

all cases of pseudotumor cerebri primarily because of the frequent finding of small ventricles, but proof had been lacking. The exact relationship between cerebral edema and papilledema in these cases is not known. For reasons stated previously, it seems most likely that the optic nerve shares in the edematous process as part of the brain as suggested by Brégeat and others rather than that the cerebral edema results in increased pressure of the cerebrospinal fluid which is then forced through the sheath of the optic nerve to press on the central retinal vein.

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SURGERY

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THE GASTRIC ANTRUM

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The Gastric Antrum. ONE of the major mechanisms controlling gastric acid secretion is mediated by gastrin release from the antral area of the stomach. The increasing number of publications in the medical literature concerning this phase of gastric secretion indicates great enthusiasm. Instead of clarification, many of these contributions have created controversy and even chaos. In an effort to realign thought in this area we have attempted a careful and extensive review of the literature.

Definition of Terms. To those uninitiated in the field of gastric physiology, the following clarification of terminology is directed:

HEIDENHAIN POUCH: a *vagally-denervated* segment of the greater curvature of the stomach (corpus) infolded as a separate pouch and drained externally through a cannula[23].

PAVLOV POUCH: a *vagally-innervated* segment of the greater curvature of the stomach (corpus) rendered separate from the main stomach by the creation of a double mucosal wall. This, too, is drained externally through a cannula.

ANTRAL POUCH: the distal 2½ to 3 cm. of stomach separated from the corpus and infolded as a pouch. It may be innervated or denervated depending upon the integrity of the vagal fibers along the lesser curvature. This pouch may be transposed to the transverse colon or to the duodenum as a diverticulum, exteriorized as a cutaneous fistula, or left *in situ*.

TOTAL STOMACH POUCH: exclusion of the entire stomach from intestinal continuity with esophago-duodenostomy. The stomach pouch is then drained externally through a cannula. This pouch may or may not retain vagal innervation.

ANTRO-NEUROLYSIS: surgical separation of the mucosa from the muscular layers of the antral area without removal of either. This is usually accom-

plished through a linear incision in the antral serosa without disturbing the extrinsic vagal fibers to this area.

GASTROJEJUNOSTOMY: anastomosis between the stomach and the jejunum without removing either.

PYLOROPLASTY: incision of the pyloric muscle with reconstruction in an attempt to enlarge the diameter of the pyloro-duodenal canal and destroy the action of the pyloric sphincter.

VAGOTOMY: severance of the vagal fibers, usually along the lower esophagus.

Anatomy of the Antrum. Many anatomical texts refer to the antral area as comprising the distal 2½ cm. of the stomach or approximately 20% of the gastric mass. This region is known to contain 1% or less of the maximal parietal cell mass of the stomach[5,11] and accordingly secretes only an alkaline mucous material[61]. Some texts state that the antrum extends along the lesser curvature to the incisura angularis and along the greater curvature to a variable and inconsistent point opposite the incisura. From the practical point of view of the surgeon operating upon this area the incisura remains an inconstant marker, its location varying with peristalic activity, the relative amount of gas in the stomach and changes in the patient's posture. Some surgeons employ a point on the lesser curvature at the junction of the first and second coronary veins as the upper end of the antral segment. Again, the coronary veins are variable and frequently obscured. The clearest definition of the antral segment has been supplied by Erik Landboe-Christensen who studied 47 human stomachs from patients of different ages and demonstrated a sharp macroscopic transition between the antrum and fundus, employing a water-acetic acid clearing method. He indicated that the antrum occupied a greater length on the lesser than on the greater curvature. His measurements demonstrated that the antrum occupies 44% of the distal portion of the stomach along the lesser curvature and approximately 12% along the distal greater curvature. Accordingly, if one is to excise the antral segment, a hemigastrectomy or 50% excision of distal gastric mass must be accomplished in order to remove satisfactorily all functioning antral tissue[53].

Gastrin. HISTORY. Pavlov in 1902[98] reported that the stimuli for gastric secretion can be divided into three phases. First of these is the psychic or cephalic phase stimulated by the smell, taste or sight of food, and abolished by vagotomy. Second, the gastric phase which stimulates the secretion of acid following the introduction of food into the stomach. It was not known whether this stimulus was mediated through a secretagogue absorbed from the food or by a hormone released from the stomach. Third, the intestinal phase, brought about by introduction of food into the small intestine and mediated either by a secretagogue absorbed from the food or by the liberation of a specific hormone.

The first reports of the existence of a gastric hormone were those of Edkins[36,37] who found that extracts of pyloric mucosa prepared in a peptone broth, in glycerine, in 3% glucose, in 5% glucose or in 0.4% hydrochloric acid would, when injected intravenously, cause the gastric glands to secrete acid. He was unable to find a secretory stimulus in extracts from the mucosa of the fundus or corpus of the stomach. Edkins called this material "gastrin" and suggested that it was the stimulus for the gastric phase of gastric secretion[37].

Zeljony and Savich[150] in studying the stimulatory effects of applications of meat extracts on the isolated pyloric antrum found that this stimulus was

prevented by cocainization of the pyloric mucosa. They felt this demonstrated that the stimulus from the antrum was actually mediated through a reflex. Ivy and Whitlow in 1922[62] were unable to substantiate a humoral phase of gastric secretion. Ten years later Priestley and Mann[101] also failed to confirm Edkins' work. It has been pointed out[141] that in both previous studies the concentration and not the quantitative output of hydrochloric acid was used as the index of stimulation. As gastric juice is produced at a relatively constant acidity, variations in acid output will be reflected mainly in volume. Babkin[5] made a similar criticism and also noted that Priestley and Mann[101] made the unhappy choice of acid gastric juice, diluted hydrochloric acid, or beef extract in hydrochloric acid as the antral stimulus, since acidification of the antrum is known to inhibit the production of gastrin[113].

In 1923, Smidt[111] reported a diminution in acid and a shortening of the second phase of gastric secretion following antrectomy in the dog. In 1925 and 1930, Ivy and Farrel[58] and Ivy[57] stated that there was a humoral phase of gastric secretion but felt that the identity of the stimulating agent was yet to be shown. His group later[104] stated that they had been able to isolate histamine from the pyloric mucosa and proposed that (1) histamine is a gastric hormone, or (2) the gastric hormone had never been extracted, or (3) there was no gastric hormone[38,79,85].

HISTAMINE. Histamine has figured prominently in discussions of gastric stimulation since Keeton *et al.*[73] showed in 1920 that histamine produces a vigorous flow of gastric juice[59]. In favor of the identity of histamine as the gastric hormone were reports[75,104] that attempts to secure a histamine-free extract of gastric mucosa had been unsuccessful. Komarov[77], however, pointed out that in both the above attempts to isolate a histamine-free extract from the gastric mucosa, the assumption had been made that the secretagogue was not a protein, and this fraction was purposely precipitated and the tests performed on the supernatant fluid (protein-free).

Against the purported identity of histamine and the humoral gastric stimulant were studies[74,82] which reported the isolation of a histamine-free gastric secretory stimulant from the liver and from the blood[125].

ISOLATION AND CHARACTERISTICS OF GASTRIN. S. A. Komarov[76,77] working in Babkin's laboratory, tried a new approach to the problem of the isolation of gastrin. Since Agren[1] had shown that secretin was a protein-like substance, Komarov felt that the failure of previous investigators to isolate gastrin might be due to their assumption that the active principle would be found in the protein-free extract of the gastric mucosa. He therefore worked with the protein fraction from the pyloric mucosa of the dog and hog. He was able to isolate a specific secretagogue which was free of histamine, choline or other organic crystalloids and had no fatty substance in it. Its chemical properties (much in common with secretin) were as follows: (a) it is a protein-like substance, (b) it is quantitatively precipitable with 10% trichloracetic acid and under some conditions with 10 to 30% sodium chloride, (c) it is soluble in 80% acidulated alcohol, and (d) it is insoluble in absolute ether, petrol ether, or absolute or 98% acetone. The differences between the chemical properties of secretin and gastrin were (1) gastrin can be precipitated quantitatively with trichloracetic acid in any stage of purification without loss of activity, while precipitation of secretin is not quantitative and is accompanied by decreased potency, (2)

there are differences in the solubilities of the two materials in methyl alcohol and ethyl alcohol[76].

Komarov felt that the material[77] he had isolated was "gastrin." He found that it was active only on intravenous or intramuscular injection and did not stimulate secretion following subcutaneous injection. This, of course, is different from histamine, and may explain why others[104] were unable to secure any gastric secretory stimulation following subcutaneous administration of their pyloric mucosal extract. Komarov's gastrin on intravenous injection was found to (a) stimulate the output of a highly acid gastric juice which was low in pepsin, (b) have no effect on the blood pressure, (c) have no effect on pancreatic or biliary secretion, (d) have no toxic effect, and (e) be free of histamine. The material stimulated flow of gastric secretion in anesthetized cats and dogs which were vagotomized and splanchnicectomized. It was also found to be effective in unanesthetized dogs, and the secretory stimulating effect was not abolished with high doses of atropine. Komarov found the highest yield of the material from the extracts of pyloric mucosa with much less from duodenal mucosa. There was little if any from the jejunal mucosa and none at all from the extracts of the mucosa of the fundus of the stomach or of the liver parenchyma.

Uvnas *et al.*[91,127] at the University of Lund confirmed Komarov's work. This group was able to extract a potent gastric stimulating agent from the pyloric mucosa of the cat, dog and pig and by better methods of chemical isolation were able to increase the potency of the isolated gastrin. The chemical properties of this material were very similar to Komarov's gastrin. Uvnas found that this protein-like substance would dialyze through a cellophane membrane, indicating that it was of small molecular size. He found that his gastrin in dry, powdered form would retain its potency as a secretagogue following a year of storage in a refrigerator. It was stable when heated to 100° C. in 0.1 N hydrochloric acid but was destroyed by heating in 0.1 N sodium hydroxide. Like secretin and insulin, this material was destroyed by ultraviolet light. It was also similar to Komarov's gastrin in its physiologic action, and Uvnas concluded that it was also identical with Edkin's gastrin.

Uvnas[128] was able to isolate gastrin in large amounts from the human pyloric mucosa and found small amounts in the human duodenal mucous membrane. Ferguson[41] extracted gastrin from the antral mucosa of patients with (1) active duodenal ulcer, (2) inactive duodenal ulcer, and (3) gastric carcinoma. He assayed the extracted material in cats and found that the secretagogue from patients with active duodenal ulcer was more than four times as potent (gram for gram of mucosa) as that of patients with gastric carcinoma or inactive duodenal ulcer.

SITE OF GASTRIN RELEASE IN THE ANTRUM. Dragstedt's group[9,10] have reported attempts to localize the site of gastrin release. Utilizing dogs with Heidenhain pouches, they created "hybrid" pouches of antral mucosa with a colonic muscle wall. Stimulation of the gastrin mechanism of the pouches resulted in a limited acid secretion. They concluded that (1) gastrin is released from one or a combination of the structures in the submucosa and mucosa of the pyloric antrum, (2) gastrin is released in the absence of antral musculature and its contained nervous structures, (3) the gastrin mechanism is viable and responsive throughout many surgical attacks, and (4) a normal gastrin mechanism requires the integrity of all layers of the

antrum. The authors suggest that the site of gastrin release might be a modified nerve cell in the submucosa and in support of this mentioned that (a) many hormones are elaborated by modified epidermal structures, (b) hormonally active tissue is frequently less histologically differentiated than other endocrine tissue, and (c) the gastrin mechanism is stimulated by acetylcholine and depressed by atropine or a local anesthetic.

Antral Stimulation. ANTRAL TRANSPLANTATION. Since 1950, primarily due to the brilliant experimental work of Dragstedt and his associates[33,34,35] knowledge has been accumulated concerning various mechanisms for stimulation of the antrum. One of the most effective maneuvers has been that of transplantation of the antral pouch as a diverticulum to other portions of the gastrointestinal tract. Using Heidenhain, Pavlov, and total stomach pouches, Dragstedt's group has demonstrated marked and sustained hypersecretion from these pouches by antral transplantation. They have further shown that ulcers can be produced at the site of gastroenterostomy by the hyperacidity secondary to antral transplantation[29,30]. Using totally isolated, vagus-denervated stomach pouches, Dragstedt[33,34] showed that transplantation increased secretion by 8- to 30-fold, even if all nervous and vascular connections with the main stomach were severed.

Botti and Hallenbeck[12] confirmed the experiments of Dragstedt's group in 1954. Others, including Harrison and associates[51] and Jones *et al.*[64,65], have employed this technique in various experimental studies with consistently effective results. In order to rule out the possibility that antral stimulation following transplantation to the colon might be due to intestinal bacteria, Oberhelman and his associates in 1952[95] treated the gastrointestinal tract of dogs with sulfasuxadine and streptomycin. They concluded that bacteria played no role in this type of antral hyperfunction. Baugh *et al.*[9,10], working in Dragstedt's laboratory in 1958, were able to show that the mucosa was the only significant portion of the antral area necessary to produce acid secretion when transplanted as a colonic diverticulum. The mechanism by which this is accomplished appears to be distention or alkalization of the antrum.

ACETYLCHOLINE. Robertson *et al.*[103] in 1950 established clearly that acetylcholine can elicit the release of gastrin from the antral mucosa by direct contact. Using denervated, isolated stomachs, divided into fundic and pyloric pouches, these investigators introduced 0.5% acetylcholine solution into the pyloric pouch for 30 minutes, causing acid release from the fundic pouch. Administration of acetylcholine by the oral, subcutaneous or fundic pouch routes failed to stimulate acid output significantly. Finally, in an attempt to determine whether the acetylcholine effect was muscarinic or nicotinic, the pyloric pouches of these animals were irrigated with 0.5% nicotine sulphate. Since no stimulation occurred, it was concluded that the acetylcholine effect was muscarinic. Many subsequent papers[9,10,84] have confirmed Robertson's observations and the employment of acetylcholine as an antral stimulator is a routine laboratory and clinical method at the present time.

FOODSTUFFS. In their original papers on the physiology of the gastric antrum, Dragstedt and his associates[34,35,95] employed various foodstuffs as test substances in isolated antral pouches, detecting the response in Heidenhain pouches or gastric fistulae. Of the substances tested, horse meat and fresh liver gave the maximum secretory response both as to volume and amount

of free acid. Aminosol, a protein hydrolysate, gave a significantly lower response, whereas milk and tap water provided little in the way of stimulation. This has been confirmed by many authors and food stimulation represents a standard laboratory and clinical method for evaluating antral gastrin release.

EFFECT OF GASTROENTEROSTOMY OR PYLOROPLASTY. The high incidence of marginal ulceration following gastroenterostomy and the advent of vagotomy (plus emptying procedure) as definitive therapy for duodenal ulceration led to the study of the effects of gastroenterostomy on acid secretion. Early work of Dragstedt and his associates[151,152] indicated that gastroenterostomy greatly increased gastric secretion when the stoma was placed in the body or fundus of the stomach but did not increase it when the stoma was located in the antral area. Schmitz *et al.*[106,107] confirmed this observation by performing gastroenterostomies which resulted in a marked increase in acid output from a Heidenhain pouch with return of the secretory level to normal range when the gastroenterostomies were taken down. They offered two explanations for this phenomenon: (1) a compensatory response of the parietal cells to neutralization beyond physiological limits (rebound phenomenon), (2) increased antral stimulation due to the repetitious passage of chyme by a circus movement via the afferent loop, carrying with it much alkalinity. In two papers in 1953, Kanar *et al.*[69,70] again pointed out the increase in acid output from Heidenhain pouches following gastroenterostomies, but contradicted Dragstedt's group by reporting that regardless of the location of the stoma there was great stimulation of acid with the highest stimulating effect occurring when the stoma was placed low in the antrum.

Harkin's group[50] made an even more extensive study of this problem employing gastrojejunostomy (two types), gastroduodenostomy (three types) and pyloroplasty (three types). In the case of gastroduodenostomy and gastrojejunostomy there was an increase in Heidenhain pouch secretion from all dogs, most prominent with gastrojejunostomy to the corpus. They noted a lesser stimulatory effect when the gastrojejunostomy was established in the antral region. In the case of pyloroplasty, a small but definite decrease in acid output was noted and they concluded that pyloroplasty was the most advantageous procedure.

LIVER HOMOGENATES. Numerous authors[10,143,144,146] have employed liver homogenates stabilized at a pH of approximately 6.3, as a stimulating agent for gastrin release. The usual technique has been profusion of the antral area with this substance. If the pH is dropped to 5 or less, the stimulatory effect of the homogenate is usually lost.

IRRITATION OR MECHANICAL DISTENTION, OR BOTH. Dragstedt's group[95] became aware of the factors of mechanical distention and irritation as one of the probable mechanisms for hypersecretion. After eliminating the possibility of bacterial contamination, this group employed various test agents in conjunction with distention and irritation of the antrum in an attempt to determine which factor was most important. They found that the introduction of liver homogenates into the pouch elicited hypersecretion in test animals. However, introduction of this material under pressure, produced the greatest stimulus to acid output. Accordingly, they concluded that increased intraluminal tension was a decisive factor in antral hyperfunction. Again in 1957[93] the same group in studying Uvnas' concept that the cephalic and gastric phases of gastric secretion were inseparable, showed that

the vagus was capable of stimulating acid secretion by increasing peristalic activity through the antrum, causing release of gastrin. Others[9,10,86,146] have confirmed these impressions.

ALCOHOL. Chittenden *et al.*[20], Ivy and McIlvain[60], and Dragstedt *et al.*[25] demonstrated the stimulatory effects of alcohol on acid secretion when this substance is imbibed or given intravenously. More recently, Woodward *et al.*[145] showed that antrectomy decreased the secretory response to alcohol and further noted that acidification of an alcoholic solution instilled into the antrum destroyed the stimulatory effect of the alcohol. Following this, others including Jordon and Sand[67,68] have employed ethanol solutions in experiments designed to determine the presence of an inhibitory hormone in the antrum capable of counteracting the gastrin release mediated by alcoholic antral perfusion.

REDUCTION OF ACID BY VAGOTOMY OR RESECTION OF THE MAIN STOMACH POUCH. In 1952, Schmitz *et al.*[106,107] showed that vagotomy to the main stomach pouch in animals prepared with Heidenhain pouches caused a marked increase in acid output. They attributed this increase to atony and stasis of food stimulating the antrum. Dragstedt and his group[39] extended this work in 1953 by showing that fundusectomy as well as vagotomy would increase acid output. Accordingly they felt that the reduction in the amount of acid bathing the antral region was the responsible agent for this increased output from the test pouch, since gastrin production continued for longer periods. A combination of decreased acid in the antrum and stasis probably is the correct explanation for this phenomenon. Thal *et al.*[123] and Storer *et al.*[120] confirmed this work.

Antral Exclusion. Since most of the complications of the Billroth II operation stem from leakage following attempts to close an indurated duodenum, it is logical in this situation to perform closure of a gastric stump proximal to the pylorus[148].

Von Eiselsberg[130] first described the operation of antral exclusion for difficult posterior duodenal ulcers. He divided the stomach near the incisura, closed the antral side, and restored continuity with a gastroenterostomy. This procedure was modified slightly by Finsterer[42] who excluded the antrum and excised a sleeve of gastric mucosa before performing the gastroenterostomy. The procedure of antral exclusion became quite popular in spite of evidence presented by von Haberer[131] that retention of the antral mucosa potentiated recurrence of marginal ulceration. Devine[22] in 1925 reported a procedure in which he divided the stomach in the mid portion and performed a gastroenterostomy. There was a 10% recurrence of melena during the postoperative period. Ogilvie[96] in 1936 advocated the use of an antral exclusion procedure similar to that of Finsterer, but 2 years later[97], noting a rate of marginal ulceration of more than 40%, stated that he realized that exclusion operations should be avoided. He postulated that the excluded antrum might be stimulated to produce gastrin by the regurgitation of bile through the pylorus.

Allen and Welch[2] reported the development of jejunal ulceration in a majority of patients whose peptic ulcer had been treated by antral exclusion, and in 1944, McKittrick *et al.*[90] described the healing of several stomal ulcers following the excision of the previously excluded antrum. Wangensteen[135] stated that the mucosa should be excised if it was necessary to leave the antrum *in situ*. Dragstedt *et al.*[27] stated that they were at first doubtful

of the proposed stimulation of the isolated antrum by means of regurgitated intestinal contents, but they demonstrated such retrograde filling of the duodenum and the excluded antrum in a patient who did develop gastrojejunal ulceration following antral exclusion. Subsequently, this group reported[141] that in dogs a barium meal can and usually does pass backwards through the jejunum, duodenum and pylorus into an excluded antrum. Marshall and Reinstine[88] reported a 54% incidence of gastrojejunal ulcer following antral exclusion and a series of 5 cases in which the marginal ulcer was cured following resection of the retained antrum. Bales and Schilling[7] chronicled the saga of a man who had 10 operations between 1919 and 1945 for peptic ulceration, among which was an antral exclusion which caused his troubles to increase. He eventually had the retained antrum excised with complete cure.

Schilling and Pearse[105] studied the effect of chronic histamine stimulation in dogs with excluded or excised antra. They found that 90% of the dogs with antral exclusion developed marginal ulcers while only 20% of antrectomized dogs developed ulceration. It seems clear that the stimulus to acid production following antral exclusion is the interference with the normal "cut off" mechanism of gastrin production normally occurring when acid gastric juice bathes the antral mucosa. Dragstedt *et al.*[33] reported that it was not necessary for the retained antrum to be in continuity with the duodenum, showing that it would stimulate acid if transplanted to the colon or to the duodenum as a diverticulum. Andersson *et al.*[3] excluded the antrum and duodenum from the gastrointestinal tract and restored continuity with a gastrojejunostomy. This antral-duodenal exclusion produced an augmentation of 24-hour secretion, a tendency to a spontaneous fasting secretion, an increased response to insulin hypoglycemia, an increased response to histamine stimulation, but did not show any change in response to a test meal.

We feel that the increased responses can be explained by 1) interference with the inhibitory function of the antrum, and 2) the probable stimulation of the antrum by regurgitated doudenal juice.

An entirely different explanation of the effect of antral exclusion has been promulgated by Waddell[132,133,134]. He felt that there is an interrelationship between the antrum and the vagus which will bring about the release of acetylcholine causing the parietal cells to produce acid. He stated that the standard procedure of distal gastrectomy is effective because it destroys the antral-vagal relationship by removing the antrum, but proposed that this disruption might be more easily effected by means of vagotomy, small sleeve resection, and antral exclusion. His hypothesis[133] is as follows:

"The antral end of the stomach acts as an important perceptive area from which afferent impulses reach the central nervous system (vagal centers) and contribute to reflex excitation or inhibition, as well as to maintain a general tonic state of the reflex center. The efferent impulses from such reflex activity are transmitted to the stomach over the vagi, and probably to a small extent over other nerve pathways, possibly the sympathetics. The final common denominator would be the liberation of acetylcholine about the parietal cells. It is believed that the rate at which this occurs is dependent in large part upon the tonic state at the reflex centers, which in turn is maintained by a continuous inflow of afferent impulses from many areas but in particular the tongue, mouth, pharynx and

the antral area of the stomach (according to the above hypothesis)."

Waddell[133] detailed the secretory studies on patients undergoing a two-stage gastrectomy in which the antrum was left *in situ* following the first stage and later excised. Acid secretory studies revealed that gastric secretion is reduced but the remaining gastric pouch is capable of responding to stimulation by insulin, peptone broth or histamine. After antrectomy this reactivity is greatly reduced or abolished. Waddell stated that the reduced reactivity is due to the removal of an important perceptive area, the antrum. The obvious question that arises concerns the pathway by which the so-called afferent stimuli from the "antral perceptor" reach the central nervous system. The procedure of antral exclusion should vagally denervate the antrum as gastric transection always denervates the pyloric sphincter. It might be argued that the only way completely to denervate the antrum is to transplant it to the subcutaneous tissue as an isolated pouch[67,68]. Certainly, however, the operative division of the lesser curvature ought effectively to block any afferent impulses from the antrum to the vagus. Chapman *et al.*[19] feel that Waddell's antral exclusion operation is unacceptable and is destined for failure, noting the occurrence of stomal ulcers in 9 of 150 patients in only 3 years.

Antrectomy. One of the earliest methods of evaluating the role of the antrum in gastric secretion was the study of antrectomy. Early reports in this field, however, do not allow the formation of any conclusion. Smidt[111], and Wilhelmj *et al.*[139] both found a significant diminution in acid output following antrectomy. Fauley *et al.*[40] and Shapiro and Berg[108,109] reported that the diminution in acid output following removal of the antrum was short-lived followed by a spontaneous return to normal levels. Further, Portis and Portis[100] and Priestley and Mann[101] found no significant change following antrectomy and felt that the antrum played no part in gastric secretion.

Woodward *et al.*[141] noted that antrectomy caused a 74% diminution in volume, a 51% diminution in the concentration of acid, and an 86% diminution in the number of milliequivalents of hydrochloric acid from Pavlov and Heidenhain pouches. They reported that partial antrectomy was followed by a decrease in pouch output only when a major portion of the antrum was excised. This statement was corrected in a later publication by the same group[95] which stated that serial partial antrectomy led to a proportionate diminution in acid output, when performed both on the antrum *in situ* and the transplanted antrum. This was confirmed by Helsby and Auten[52] who also reported that total antrectomy almost completely abolished Heidenhain pouch output. This view was later expressed by Baugh *et al.*[10] who added that exclusion of the antrum markedly diminished Heidenhain pouch output. Botti and Hallenbeck[12] did not agree. These investigators studied the effect of antral transplantation to the colon or duodenum, and found that subsequent exteriorization or excision of the antrum led to an equal diminution of pouch output. They noted the discrepancy between their work and that of Dragstedt's group[95], and Helsby and Auten[52], and stated that they felt this was due to the removal of fundic mucosa along with the antral pouch by the others.

The effect of antrectomy in conditions of chronic antral hyperstimulation (such as antral exclusion or gastroileostomy) has been demonstrated. Bravo *et al.*[13] reported a study in which Heidenhain pouches were created and

then drained internally into the ileum. In some of these animals an antrectomy was done and in others the antrum was transplanted to the colon. Peptic ulceration developed in the control animals (antrum *in situ*) and in the antrum-transplanted animals, but the antrectomized dogs showed no ulceration.

Dragstedt's group has reported studies on the effect of antrectomy on the total innervated gastric pouch. In the earlier study[31] they found a 10 to 15% decrease in daily gastric acid following antrectomy, and reported the removal of the antrum caused a significant diminution in the acid produced in response to insulin hypoglycemia. Later[102], they found that antrectomy produced no constant pattern in relation to the acid response to food intake and to insulin hypoglycemia. However, they did find that antrectomy caused a very significant increase in gastric acid output of the total isolated innervated gastric pouch to histamine stimulation. Woodward *et al.*[141] found that antrectomy did not consistently alter the pouch response to histamine stimulation in Pavlov and Heidenhain pouch dogs. Langlois and Grossman[78] divided the stomach into two pouches, pyloric and fundic, and found that removal of the pyloric pouch caused no change in the response to histamine. Finally, Waddell[133] stated that removal of the antrum in humans is almost always followed by profound diminution in the response to histamine, contrary to all of the above opinions.

Stubbe[122] recorded gastric secretory data on 39 patients with peptic ulcer who were treated by excision of the antrum and first part of the duodenum. He found little apparent change in gastric secretion in the early postoperative period, but noted a gradual diminution of acid over the succeeding months without a decrease in pepsin activity. He stated that since many patients were found to have a postoperative gastritis, this might be the mechanism for the postoperative diminution in acid.

Antral Inhibitory Hormone. HISTORY. Babkin[5] states that Solokov found that the output of acid from a Pavlov pouch was diminished following the introduction of 0.5% hydrochloric acid into the stomach or following introduction of gastric juice into the duodenum. Working on the problem of duodenal inhibition, Pincus *et al.*[99] showed that there was no inhibition of acid output following instillation of hydrochloric acid into the duodenum until the pH reached 2.5 or lower. Wilhelmj *et al.*[138] then demonstrated that the gastric phase of acid secretion was inhibited by the introduction of acid into the isolated total stomach pouch. Brunschwig *et al.*[15] injected normal human and dog gastric juice intravenously into dogs and found that this acted as a gastric secretory depressant. This substance was not present in the gastric juice of humans with pernicious anemia or with gastric carcinoma. Hood *et al.*[55] compared the inhibitory action of canine gastric juice collected from fundic and antral pouches. The major portion of the inhibitor came from the antral pouch. A common objection to both these experiments is that pyrogenic material was injected intravenously making the results difficult to interpret.

Woodward *et al.*[143] in 1954 using dogs with isolated antral pouches found that the increased Heidenhain pouch output following histamine administration was not inhibited by irrigation of the isolated antral pouch with 0.1 normal hydrochloric acid. This occurred even though the stimulus of irrigation of the antrum with liver homogenate could be inhibited by decreasing the pH of the homogenate from 6.3 to 5. In dogs with the stomach

intact but with the antrum isolated and drained via a duodenal fistula, it was found that the normally high spontaneous gastric secretion was inhibited by antral perfusion with 0.1 normal hydrochloric acid. After this, 10 units of insulin were given intravenously and the acid output was greatly increased in spite of continuous antral irrigation with hydrochloric acid.

In attempting to determine whether antral inhibition was due only to a suppression of gastrin formation or whether there was a true inhibitory hormone, Harrison, Lakey and Hyde[51] designed an ingenious experiment. They prepared Heidenhain pouch dogs and transferred the distal one-half of the gastric antrum to the colon as a diverticulum, leaving the proximal half *in situ* and anastomosing this to the proximal duodenum. It was found that excision of the gastric portion of the antrum caused an average increase of acid output of 62%. Removal of the remaining colonic diverticulum caused the gastric phase to be almost totally abolished. Harrison concluded that the portion of the antrum left in continuity with the stomach was producing an inhibitory hormone in response to the increased acid output following antral transplantation. When the portion of the antrum in continuity with the stomach was excised, this inhibitory hormone was lost, and the acid output consequently increased. The suggested mechanism of inhibition was either interference with gastrin production, a chemical neutralization of gastrin or a direct action on the parietal cell. Dragstedt's group[86] was unable to duplicate this work. They prepared dogs with two separate denervated antral pouches, both isolated. When liver homogenate was introduced into either pouch, the acid output was stimulated. They then stimulated the gastric phase by instilling 3% "liver solution," pH 7, into one antral pouch, replacing it every 15 minutes. After a vigorous acid secretion was stimulated, periodic irrigations of the other isolated antral pouch with 0.2 normal hydrochloric acid did not cause a diminution in acid output. The stimulation and inhibition were alternated between the two pouches and there was no change noted. This experiment was repeated leaving the vagal innervation of the two antral pouches intact. The increased acid output resulting from instillation of 3% "liver solution" into one antral pouch was still not inhibited by instilling 0.2 normal hydrochloric acid into the other. This was also the case when the stimulus to gastric secretion was 0.5% acetylcholine.

Jordan and Sand[67,68] prepared Heidenhain pouch dogs with two longitudinally divided, isolated antral pouches, both made into cutaneous fistulae. Gastrin production was stimulated by irrigating one pouch with 10% alcohol over the entire experimental period. After acid output was obtained, the second pouch was irrigated with 0.1-normal hydrochloric acid. In the majority of perfusions, the Heidenhain pouch output was inhibited following acid irrigation of the antral pouch. These investigators then attempted to inhibit the gastric secretion stimulated by histamine by acid irrigation of an isolated antral pouch. In the majority of experiments, they obtained a diminution in pouch output. The most significant data in the latter experiment were the differences in Heidenhain pouch output following histamine stimulation when the isolated antral pouch was irrigated with acid as opposed to washing with physiologic saline solution.

Dragstedt's group[86] noted many objections to these studies. Primarily, they stated that alcohol is a poor stimulus, as repeated irrigations of the pouch may lead to sufficient absorption

of alcohol into the blood to cause a direct stimulation of the Heidenhain pouch. This seems to be an invalid criticism since direct stimulation of the pouch would make inhibition even more difficult to demonstrate. Second, they noted that periods of from 1 to 3 hours of acid irrigation of the antral pouch were required in order to suppress Heidenhain pouch output, whereas the inhibition following introduction of acid into an antral pouch comes about within a matter of a few minutes in their experiments. Lastly, they wonder if the saline used to remove acid solution did not increase the Heidenhain pouch output by stimulating gastrin release secondary to distention of the antrum.

Ragins *et al.*[102], working with vagus-innervated, total gastric pouch dogs, attempted to clarify the question of antral inhibition. After histamine stimulation, the dogs were antrectomized and 8 of 9 dogs increased their acid output from 1 to 83%. The authors had some difficulty explaining this stimulation following antrectomy, but did state that such an effect was compatible with the release of an inhibitory substance from the antral mucosa on contact with acid. (This is the only statement from Dragstedt's group that an inhibitory hormone may indeed exist.)

Gouws and Harrison[45] found that the vagus was not involved in antral inhibition of gastric secretion. They repeated their previous work[51] taking care that the vagal innervation of the proximal antrum was undisturbed. Following the collection period, the antrum was denervated by transecting the stomach proximal to the antrum, stripping the serosa and then resuturing in continuity. They found no change in the Heidenhain pouch output. Following this, the proximal (gastric) half of the antrum was excised, and again they found the Heidenhain pouch output was increased.

Margolus and Harrison[87] studied antral inhibition in the Heidenhain pouch dogs with the antrum excluded from the stomach and brought out as a cutaneous fistula. In these animals, acid output following the ingestion of food is thought to be a reflection of the intestinal phase of gastric secretion. The response of the Heidenhain pouch to the stimulus of a standard meal, during which the isolated antrum was irrigated with either physiologic saline solution or 0.1 normal hydrochloric acid, was noted. Perfusion of the antral pouch with 0.1 normal hydrochloric acid resulted in a diminution of acid output. This was interpreted as demonstrating that an antral hormone was produced which acted to inhibit the intestinal phase of gastric secretion.

Shimizu, Morrison and Harrison[110] studied the inhibition of vagally stimulated gastric acid by the antrum. In dogs with a Hollander pouch (vagally innervated), isolated antral pouches were prepared as cutaneous fistulae. In 2 animals, vagal innervation to the antrum was preserved, and in 2, it was severed. The animals were given insulin and the isolated antra irrigated with hydrochloric acid. There was an inhibition of Heidenhain pouch output in dogs with both the innervated and the denervated antra and the authors concluded that the antrum when irrigated with hydrochloric acid can inhibit acid formation stimulated by the vagus whether or not the innervation of the antrum itself is intact[56].

State and Morgenstern[117] found that they could secure an inhibition of Pavlov pouch output with acid irrigation of the isolated antrum. It should be noted that these investigators found a definite diminution in Pavlov pouch output when they irrigated the antral pouch with saline. The authors stated

that the inhibition of Pavlov pouch output following acid irrigation of the isolated antrum must be due to release of a hormone. Since the antrum had not been stimulated to liberate gastrin, this inhibitory substance must have acted to decrease acid production directly rather than by suppression of gastrin formation. Further, they stated that this suppression could not be due to a reflex such as Code and Watkinson[21] mention as the mechanism of duodenal inhibition, since the antral pouches were denervated.

Woodward *et al.*[149] were unable to repeat the work of Harrison *et al.*[51] but did find that perfusion of the antrum with hydrochloric acid during histamine stimulation caused a diminution of Heidenhain pouch output by 50%, but only after 1.5 hours of irrigation. This worked as well with the innervated as with the denervated antrum. In studying the effect of antral perfusion with acid on the intestinal phase in the Heidenhain pouch, isolated antral pouch dogs, Woodward *et al.*[149] found that acid perfusion of the denervated antrum caused no decrease of acid output. However, in one animal with an innervated antrum, acid perfusion did suppress the Heidenhain pouch secretion. This the authors were unable to explain. They stated that they had previously missed the inhibiting effect of acid in the antrum because of inadequate duration of perfusion (minimum of 2 hours). They felt that acid to the antrum will immediately stop acid output due to gastrin stimulation. However, it took 1½ to 2 hours to inhibit the acid output following the stimulus of histamine or the intestinal phase. They concluded that inhibition by the antrum is slow and inconstant, needing a high acid concentration to trigger it, and stated that an intact antrum is not beneficial.

Dragstedt *et al.*[28] reported another attempt to repeat the work of Harrison *et al.*[51]. Dragstedt noted that some of the dogs did show an increased secretion following excision of the gastric antral remnant but that there was a significant increase in acid output following excision of a portion of the proximal stomach (acid secreting region), along with the gastric antral remnant. Evans *et al.*[39] had found that excision of the fundus of the stomach in Heidenhain pouch dogs caused a great increase in acid output, this supposedly due to the lack of acid inhibition of the antrum. In the current study, Dragstedt explained the results of increased Heidenhain pouch output following resection of the gastric antral remnant (along with a part of the proximal stomach) by stating that the increase was due to a lack of duodenal inhibition. He further suggested that the increased output noted by Harrison *et al.* could be explained on this basis.

Conclusion. Results of conflicting experiments are difficult to interpret but it seems probable that the antrum does elaborate a separate inhibitory hormone. The significance of this is not known even in experimental laboratory preparations, and it is impossible now to assay its importance in humans.

This subject is of obvious clinical importance and efforts to isolate such a hormone should receive priority in further work. The isolation of a potent inhibitor of gastric secretion would revolutionize the care of peptic ulcer patients.

Effects of Drugs on the Antrum. These are presented in Table 1.

Antral-Vagal Interrelationships. Shortly after the acceptance of gastrin as a substance capable of stimulating secretory activity in the parietal cell mass of the stomach, there arose the inevitable controversy concerning the interrelationship between the cephalic or vagal influences and the gastrin or

TABLE 1.—EFFECTS OF DRUGS ON THE ANTRUM

Drug	*Concentration Employed*	*Route*	*Action*	*Latent Period*	*Reference*
Acetylcholine	0.5% to 2%	Local application	Stimulatory	10–30 mins.	9, 10, 84, 103
		" "	None	—	103
Nicotine	0.5%	" "	Stimulatory	Immediate	67, 68, 145, 146 147
Alcohol (Ethyl)	5% to 10%	" "	Stimulatory		144
Sodium Bicarbonate		Systemic	Stimulatory	60–80 mins.	3, 46, 63, 110, 132
Insulin	10–20 u.	Subcutaneous	None	—	3, 46, 74, 75, 132
Histamine	0.5 mg.	Local appl. and systemic	None, unless high concn. used which destroy antral mucosa	—	72
Antihistamine	Variable				
			Inhibit	Immediate	143, 146, 150
Local anesthetics (Cocaine, Procaine etc.)	2 to 2%	Local appl.			
			Inhibit	Immediate	4, 9, 10, 143, 150
Atropine	1% solution or 0.3 mg. S.C. 0.2 mg.	Local appl.			

humoral influences on acid peptic secretion by the stomach. In 1933, Straaten[121] postulated that the cooperation of the pyloric part of the stomach was essential to the secretory activity of the vagus nerves. Noring[92] and Lim and Mozer[81] concurred in this opinion. Subsequently, Uvnas[126], in an excellent experimental study, confirmed Straaten's work, concluding that vagal stimulation during the neural phase of gastric secretion leads to the release of gastrin. He showed that electrical stimulation of the cervical vagi caused acid secretion which was greatly diminished if the pyloric region was deprived of its arterial blood supply, if its venous outflow was obstructed, if the function of the pyloric mucosa was depressed by cocaine, or if the pylorus was excised. Further, in cross-circulation experiments he demonstrated that a gastric secretory agent was liberated from the pyloric region during vagal stimulation.

The data reported by Uvnas were not compatible with the results achieved by other investigators, notably Babkin *et al.*[6] who in 1944 repeated the Uvnas experiments. They found that the vagus was able to convey strong secretory impulses to the gastric glands despite antrectomy. Following antrectomy there was usually an inhibition of gastric secretion induced by stimulation of the vagus nerves, but this secretory depression lasted only a few hours before returning to preoperative levels. The more crudely the stomach was handled, the greater and more prolonged was the inhibition of the gastric secretion. These authors presumed that the inhibition was due to hyperactivity of the sympathoadrenal system incident to operative trauma alone.

Because the results of Babkin *et al.* did not agree with those of Uvnas, despite similar experimental conditions, the entire problem was reinvestigated by Linde and reported in his monograph in 1950[83]. Working with cats, Linde partially confirmed Uvnas' conclusions that the cooperation of the antrum was important to the secretory activity of the vagus nerve. He felt that there was a synergistic cooperation between the vagal secretory and the humoral mechanisms of acid secretion. He did, however, point out that the integrity of the antrum was not a *sine qua non* in the process of secretion during vagal stimulation. During some experiments he was able to produce a small but distinct amount of secretion even after resection of the antrum.

The confirmatory work of Linde was quickly countered by Janowitz and Hollander[63] who, in 1951, presented what they considered critical evidence that vagal stimulation did not release gastrin. These authors stimulated the vagus after esophagostomy, by sham feeding and by insulin injection, pointing out that the Heidenhain pouch failed to secrete acid in 15 separate experiments despite intense vagal stimulation. Oberhelmen *et al.*[93,94] observed the same phenomenon many times and agreed with Janowitz and Hollander.

Grossman[48] and Langlois and Grossman[78] also favored the view held by Janowitz and Hollander. However, Glass and Wolf[44], working with normal and duodenal ulcer patients both before and after gastric resection, found that the antral area was involved in the acid secretory mechanism following vagal stimulation. They used insulin hypoglycemia as their test method with collection of samples for analysis as to acid, pepsin and gastric muco-protein. Arey *et al.*[4], again working with normal and ulcer patients, employed atropine sulphate as a vagal blocking agent and failed to agree with Glass and Wolf. The methods of collection and the failure to control the intestinal phase

of acid secretion mediate against definitive statements in both human experiments.

In an attempt to resolve this controversy, Dragstedt and his group in a series of papers[31,33] using vagally innervated, total stomach pouches showed that antral resection resulted in a very small reduction in acid secretion. He explained this 10 to 15% decrease in acid output by the removal of some acid-secreting cells inadvertently during the process of antral resection. In the same dogs, with division of the vagi to the pouch, a profound decrease in secretion resulted. A similar decrease in output of acid from a vagus innervated, total stomach pouch was noted following division of the vagus nerves even though the antrum remained a part of the isolated stomach. Thus, he concluded, the antral mucosa is not essential for vagus secretory function and the effect of vagus secretory impulses is not mediated through the liberation of gastrin.

Schmitz *et al.*[106,107] and Evans *et al.*[39], in 1952 and 1953, were unable to show that antral function was dependent in any way on vagal stimulation. They did demonstrate, however, that the absence of vagal stimulation decreased the acidity in the antral region causing a profound increase in Heidenhain pouch output. They attributed this effect to the decrease in acidity of the main pouch, which prolonged the gastrin stimulating mechanism, and to the atony and dilatation of the stomach with stasis.

Burstall and Schofield[16,17] reported that both psychic stimulation and insulin hypoglycemia produced a small but detectable increase in secretion from the Heidenhain pouch if special methods were employed for the determination of the small amounts of acid. The authors stressed that this response could be due to vagus innervation reaching the pouch along the blood vessels of the greater curvature or to the effect of gastrin released from the antrum; the latter possibility appeared to be more probable. They pointed out that sham feeding was a more effective stimulus than insulin hypoglycemia.

Dragstedt and his group[32] demonstrated that antral motility, as a result of vagal stimulation, might be the factor by which this dilemma could be resolved. They noted that as early as 1925, Lim *et al.*[80] and later Grossman *et al.*[49] found that antral distention caused an increased acid output from pouches even if the antrum or the fundus were transplanted subcutaneously. Accordingly, they showed that a primary factor in gastrin discharge from the antrum was increased intraluminal tension due to peristalic activity within the isolated antral segment. It seemed reasonable therefore to believe that whatever small response occurred in the way of gastrin release due to vagal stimulation could be attributed to the increased peristalsis produced by the vagus effect on motility.

Again in 1956, Uvnas' group[129] used the antral-vagal interrelation to explain their findings in Heidenhain pouch dogs with antrum-duodenal exclusion. In the same year Waddell[133] postulated his unique hypothesis (see above).

After deciding that the common denominator of antral-vagal relation was peristalsis caused by vagal stimulation, Dragstedt and his group[26] and Woodward *et al.*[144] published papers in 1957 defining the stimuli responsible for antrum motility. Dragstedt concluded from this work that Uvnas was partially correct in his original deductions in 1942, in that vagal stimulation causes acid output by liberation of gastrin following antral stimulation by increased peristalsis secondary to motor vagal discharge.

Motility studies in humans by Hightower and Code[54] and Smith and Code[112] have confirmed the increased antral motility following numerous stimuli.

As a natural outgrowth of the study of antral-vagal interrelationship it seemed reasonable to investigate the precise mechanism by which nervous control was exerted on the antrum. Baugh *et al.*[9,10] excised the antral mucosa in Heidenhain pouch dogs and created a colonic diverticulum of colon mucosa covered by antral musculature and serosa. This resulted in a significant decrease in acid output. They then excised the antral musculature in other animals and replaced it with colonic musculature leaving the antral mucosa intact and in place. Again this resulted in a decrease in Heidenhain pouch output. Transplantation of the "hybrid" antrum to the colon yielded an increased acid output similar to the control level but less than the hypersecretion caused by transplantation of the normal antrum to the colon. The "hybrid" antrum was then removed from the colon and brought out as a fistula and found to be sensitive to stimuli. Distention of this pouch did not stimulate secretion.

In 1957, Jones *et al.*[64] performed antro-neurolysis by dividing the antral wall through its submucosal layer, thus lysing Meissner's plexus. In the animals with Heidenhain pouches, a definite and significant drop in acid secretion occurred, but in animals with Pavlov pouches, a distinct rise in output was apparent. This was explained as a disturbance of the intrinsic reflex pattern with antro-neurolysis, thus preventing gastrin release and stimulation of the Heidenhain pouch. The increased secretion of the Pavlov pouch was not adequately explained. This group postulated that antral function is an expression of an intact, independent neurohumoral organ under partial control by parasympathetic and sympathetic nerves.

DeVito *et al.*[24], working with antro-neurolysed dogs, confirmed the above results. They then performed gastroenterostomy, bilateral thoracic vagotomy, or transplantation of the neurolysed antrum to the colon in these animals. The animals subjected to gastroenterostomy had a transient rise in acid output. Vagotomy increased the pouch output to the pre-antro-neurolysis level, and with antral transplantation to the colon there was a very marked elevation of pouch output with one dog perforating a peptic ulcer. They concluded that antro-neurolysis decreased gastric output by interfering with a local reflex mechanism. Further, they felt that the vagi, following antro-neurolysis, are inhibited by an intact myenteric plexus. They felt that antro-neurolysis raised the threshold for gastrin response or increased the sensitivity of the gastrin mechanism to acid inhibition.

Jones *et al.*[66] in 1958 concluded that vagal inhibition of the distended antrum is greater than any hormonal stimulating influence. They created an isolated antral pouch and transferred it to the transverse colon as a diverticulum with innervation intact. Denervation of the diverticulum caused an increase in acid output. They then reattached the denervated pouch to the stomach and lastly excised the pouch and discarded it.

Gouws and Harrison[45] in attempting to determine whether the stimulatory or inhibitory functions of the antrum were dependent on intact vagus supply, created Heidenhain pouch dogs with isolated antra. The antral pouch was exteriorized as a fistula, stimulated by food, alcohol and distention and inhibited by acid, before and after vagotomy. Their studies indicated

there was no change after vagal section, concluding that vagus innervation was not mandatory for antral function.

Thal, Perry and Wangensteen[123], in attempting to evaluate the various operative procedures for patients with duodenal ulceration, studied the innervated and denervated antrum in the so-called "tubular" and "segmental" types of gastrectomy. Their studies indicated that an innervated antrum is capable of producing marked acid output while a denervated antrum becomes much less sensitive to stimulation and causes a significant decrease in acid output under their test conditions. This is in distinct opposition to the views of Gouws and Harrison. Perhaps this difference can be best explained by the type of preparation used in both groups. Wohlrabe and Kelly[140] working with Heidenhain pouch dogs with isolated antra drained externally, supported Wangensteen's view. They demonstrated that vagal denervation of the isolated antrum resulted in a moderate decrease in acid secretion and further pointed out that cholinergic stimuli appeared to act directly upon the cell responsible for the release of the antral hormone since this response is not significantly blocked by cocaine.

The last word in these many disputes has not been spoken. Most recently, Thein and Schofield[124] still attempting to substantiate Uvnas' original work, have provided evidence suggesting the release of gastrin from the antrum following vagal stimulation by sham feeding. Using a completely denervated corpus pouch transplanted into the musculature of the abdominal wall, they were able to elicit a response to sham feeding of significant degree, capable of being potentiated by Urecholine. This response was abolished by denervation or acidification of the antrum and suggests that the vagus can release gastrin from the antral area.

Conclusion. In concluding this section it seems clear that there is a definite antral-vagal interrelationship, the significance of which has not been evaluated satisfactorily. We feel that this interrelationship is two-fold. First, vagal stimulation causes an increase in peristalic activity in the antrum which is responsible for gastrin stimulation. Secondly, there resides within the submucosa of the antrum a reflex mechanism of nervous origin capable of stimulating the gastrin secreting cells. This reflex is partially controlled by the vagus and perhaps other nervous afferants. Obviously further work must be done to clarify this latter point.

Antral-Pancreas Interrelationship. Barcena *et al.*[8] found that total pancreatectomy had no effect on the output of gastric acid by the Heidenhain pouch.

Brooks[14] prepared Mann-Williamson dogs, waited for the development of duodenal ulceration, and then anastomosed the pancreatic duct to the antrum. In most dogs, the ulceration healed. The author stated that the effect of the anastomosis was to (1) stimulate the antral phase of gastric secretion because of the alkalinity of the pancreatic juice, and (2) to act as a hydrochloric acid buffer. Since the healing was almost uniform, the second factor must outweigh the first.

Sokolov[113] in 1904 first demonstrated that gastric juice in the duodenum causes a decreased output of acid. Griffiths[47] found that hydrochloric acid in the human duodenum diminished the acid response to an alcohol test meal. Greenlee *et al.*[46] felt that the duodenal inhibition of acid output may be due to the release of pancreatic secretin. They injected secretin intravenously into a Heidenhain pouch dog and found that this did decrease the

acid output with a simultaneous increase in the flow of pancreatic juice. Secretin was found to abolish the Heidenhain pouch response to a test meal, but to have no effect upon the output of an innervated total gastric pouch stimulated by insulin, indicating that the cephalic phase was not affected by secretin. There was no change in the histamine effect on Heidenhain pouch dogs following the injection of secretin. Heidenhain pouch dogs were created with innervated, isolated antral pouches and were found to respond with an increased acid output to the administration of insulin or to a test meal. This was thought to be due to an increase in antral motility. This increased acid output was blocked with intravenous secretin showing that it was possible to suppress gastrin release following mechanical or chemical stimuli. In similar dogs, irrigation of the antrum with a 3% "liver solution" resulted in an increased Heidenhain pouch output. This was abolished by feeding the animal an acidified meal. The authors felt that this was due to a release of endogenous secretin. They felt that the intestinal phase was not inhibited by secretin because of the spontaneous return of acid output in 2 hours after food, even if the intravenous administration of secretin was continued.

Antral-Intestinal Phase Interrelationship. Dragstedt[26] stated that the intestinal phase is due to a release of a gastrin-like substance from the intestinal mucosa after contact with whole or split protein. It has been repeatedly shown that introduction of acid into the duodenum will inhibit gastric acid output[21,91,113]. Dragstedt[33] working with isolated, vagus denervated, total stomach pouches concluded that the intestinal phase accounted for less than 5% of the total output of acid. The relative importance of the various phases of gastric secretion is difficult to assess as it is necessary to interfere with one phase in order to study another.

The output of acid from the Heidenhain pouch of dogs with excised or isolated (non-stimulated) antra is a function of the intestinal phase. Such preparations have been used to study inhibition of the intestinal phase following application of acid to the antral mucosa. Woodward *et al.*[143] found an increase in acid in 1½ to 2 hours after feeding and stated that application of 0.1-normal hydrochloric acid did not affect this flow. On the other hand, Margolus and Harrison[87] found that the acid output in Heidenhain pouch, isolated antral pouch dogs was between 72 and 222 mEq. per L. and that this dropped to 0 to 14 mEq. per L. when the antrum was irrigated with 0.1 normal hydrochloric acid. Antral irrigation with saline had no effect. Woodward *et al.*[149] reported that they were unable to suppress the intestinal phase of secretion by irrigating the denervated antral pouch with hydrochloric acid but did almost completely stop acid output in one animal by the irrigation of an antral pouch to which the vagal innervation had been preserved. They were unable to explain this, and doubted that the intact innervation was significant.

The problem of "spontaneous secretion" is frequently mentioned in studies dealing with the isolated antrum[3,143,144,149]. Woodward *et al.*[144] felt that this is due to the irritative mechanical stimulation of an indwelling cannula. We feel that another obvious source is the regurgitation of alkaline duodenal contents across the pylorus if any part of the duodenum is in continuity with the isolated antrum.

Protective Role of Antrum in Ulcer Surgery. Since the antrum acts to suppress the gastric phase of acid secre-

tion when the antrum mucosa is bathed in acid, an argument can be made that it is safe to retain the antrum if it is left in continuity with the gastric pouch. Wangensteen[136] took great pains to differentiate between antral exclusion and the retention of the antrum in continuity with the residual gastric pouch. He devised the segmental gastric resection, in which the mid-portion of the stomach was excised leaving only small stumps of the proximal and distal end which were anastomosed to one another, followed by pyloroplasty. State *et al.*[115] found that dogs with a 50% sleeve resection were much more resistent to the ulcerogenic action of histamine than were control dogs with a 50% Billroth I or Billroth II gastrectomy. However, when the dogs with segmental resection were then subjected to antrectomy, 2 of 3 developed ulceration[116]. Kaplan and State[71] repeated these experiments substituting segments of jejunum or colon in some of the antrectomized dogs. Animals with interposition had a high incidence of ulceration demonstrating the specificity of the protective action of the antrum in continuity.

Byrd and Sawyers[18] contrasted the effects of histamine administration in dogs with 50% gastrectomy, half of whom had the antrum in continuity, while in the others the antrum was left as a diverticulum. The incidence of peptic ulceration in the dogs in which the antrum was left as a diverticulum was four times greater, indicating to the authors that the antrum must be in continuity between the fundus and the duodenum in order to exert its protective action.

Critique. Throughout the experimental work in this review, many discrepancies can be attributed directly to technical features inherent in the animal preparations. We would like to point out the following major stumbling blocks which have rendered some experimental work useless and others open to great criticism:

(1) The inability to differentiate between antrum and fundus. Since there is no very obvious, clear-cut separation of these two areas of the stomach, it seems reasonable after separating that portion assumed to be antrum, to then amputate a 0.5 cm. area from the divided antrum and from the residual fundus for careful histologic study. In this manner, and in this manner only, can one be assured that an antral pouch contains no parietal cells and that the residual pouch contains no antral mucosa.

(2) Unwarranted conclusions made from experiments employing too few animals or from those in which the animals were subjected to prolonged or extensive manipulations.

(3) The failure of mucosal bridges. All too often, in our experiments as well as those of others, mucosal bridges have broken down with the result that incorrect conclusions have been drawn. It is advocated that all animals be periodically tested for the integrity of a mucosal bridge, using methylene blue or some other dye, and that at the conclusion of the experiments the animals be sacrificed and the bridges carefully examined.

(4) The lack of standardization of of dietary intake. It is well known that varying the diet of dogs and other animals employed for experiments in gastric physiology will result in abnormal acid output. It is suggested that some standard program be adopted and that a careful survey of the actual amount of food taken by the animals and the amount of vomitus be recorded. Further control periods of many weeks should be employed before actual experimental work is started.

(5) The relative effect of cannulae

and reflux of intestinal secretion. The presence of mechanical devices or of regurgitated intestinal juices in the antrum probably results in the so-called "spontaneous secretion" from various stomach preparations. This pitfall must be carefully avoided whenever possible.

(6) Species differences. Variations among species must be taken into account in any animal work. The transferral of information from one species to another without supporting experimental data should be discouraged.

(7) Difficulties with human experiments. Because of the many difficulties in standardization and collection, most previous studies in humans are of little value.

Summary. A comprehensive review of the gastric antrum and its physiology has been set forth.

The antrum remains the least understood area of the stomach and is thought by some[114], including the authors, to hold the key to the surgical approach of ulcer in the future.

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BOOK REVIEWS AND NOTICES

A Textbook of Neurology. By H. Houston Merritt, M.D., Professor of Neurology, Columbia University. 2nd ed. Pp. 765; 182 ills. Philadelphia: Lea & Febiger, 1959. Price, $12.50.

To his knowledge, in the humble opinion of this reviewer, this is the best textbook of neurology available. It is complete enough to satisfy the appetite of even the most avid third or fourth year medical student. If it is not, the latter can find enough references at the close of each communication to serve as a jumping off place for further reading.

Particularly appreciated by this writer are the many tables which set down percentages. These eliminate some of the vagueness and general impressions which appear in some other texts. The author, an eminent man in his field, speaks with the understanding and authority not only of experience but of figures.

New considerations of mucormycosis, echo viruses, cat scratch fever, cervical spondylosis, leukemia and thrombotic thrombocytopenic purpura have been added. Other conditions have been reclassified so that now more diseases are brought into the group of metabolic disorders from the degenerative which so often is a cover for ignorance. As in the earlier edition all diseases are presented on an etiological basis. An extensive index is provided.

Still absent are two discussions that this reviewer considers should be included in a textbook such as this: a brief description of how the examination of the nervous system is performed and an outline, at least, of the neuroses which so often come up for differential diagnosis when organic neurological diseases are concerned.

This book is heartily recommended for all who treat or contact diseases of the nervous system. S.G.

Myasthenia Gravis. By Kermit E. Osserman, M.D. Pp. 286; 58 ills. New York: Grune & Stratton, Inc., 1958. Price, $10.00.

This is an excellent monograph on myasthenia gravis. The author has combined an extensive personal experience with information gained from a comprehensive review of the literature and produced an authoritative summary of the present knowledge concerning this disease. After an interesting historical chapter, the pathology, physiology, and clinical aspects are presented. These chapters are followed by discussions of diagnosis, treatment by specific drugs, and supportive measures including nursing care. In addition, consideration is given to special features, namely the endocrine, obstetric, and pediatric, as well as to the question of thymectomy or radiation to this gland. Finally, the reasons for a more hopeful outlook for patients with myasthenia gravis are given.

This book is recommended to all physicians who are concerned with this difficult disease problem. C.Z.

Annual Review of Biochemistry, Vol. 27, 1958. Edited by J. Murray Luck, Frank W. Allen and Gordon Mackinney. Pp. 775; illustrated. Palo Alto, Calif.: Annual Reviews, Inc., 1958. Price, $7.00 (U.S.); elsewhere $7.50.

The latest in this highly regarded series of Annual Reviews of Biochemistry continues to provide surveys of principal advances in the areas which are customarily reviewed. These include: Chemistry of the Carbohydrates; Carbohydrate Metabolism; Newer Developments in Relation to Protein Biosynthesis; Biochemistry of Protein Hormones; Amino Acid Metabolism; Biosynthesis of Cholesterol; Nutrition; Water Soluble Vitamins; Fat Soluble Vitamins; Biochemistry of Viruses; Biochemistry of Cancer; Biological Oxidations; and Proteolytic Enzymes.

In addition, there are timely reviews of: Enzymatic Metabolism of Drugs and Other Foreign Compounds; Chemistry and Biochemistry of Antibiotics; Metabolic Antagonists; and Enzymology of Nucleic Acids, Purines, and Pyrimidines.

There is also an interesting special chapter "Impressions of an Organic Chemist in Biochemistry," by H. T. Clarke.

This volume will be welcomed by biochemists and others engaged in teaching and basic research. Clinical investigators will also find much that is useful in these reviews. C.Z.

Problèmes D'Organisation et de Fonctions Chez les Bactéries et les Virus. Edited by J. André Thomas, La Sorbonne. Pp. 386; 154 ills. Paris: Masson et Cie, 1958. Price, 5.000 fr.

THIS is the fourth of a series of monographs on cellular physiology under the editorship of Dr. Thomas. The first, published in 1955, dealt with the functions of the structures of mammalian cells in general, the second with cell growth, and the third with microbial genetics. In the present monograph the subject is again the relationship of structure to cellular economy, but this time it is limited to bacteria and viruses.

The section on bacteria begins with a summary of the nature of the bacterial cell by A. R. Prévot. This is spotty; some topics, for example mitochondria, are scarcely mentioned at all. The same author follows with a classification of bacteria embodying his well-known opinion that anaerobes deserve a larger place than that assigned to them by Bergey. Giroud and Dumas' chapter on Rickettsiae, Bartonella and the Pleuropneumonia group is well done, as are the chapters by Hauduroy on filterable cycles and L forms. Finally, Vendrely presents a very good review of nucleoprotein metabolism.

The section on viruses contains three chapters. The first, by Barraud, describes the contributions of crystallography to the study of virus organization. Next is a review of the antigenic properties of bacteriophages and representative animal viruses by Hannoun, and this is followed by Lepine's chapter on virus synthesis.

For the most part the authors are writing from long research experience. Consequently their contributions are well worth reading and deserve a place on reference shelves. The illustrations are excellent and they are reproduced on high gloss paper. The binding is weak. E.S.

CLINICAL CHEMISTRY IN PRACTICAL MEDICINE. By C. P. STEWART, D.Sc. (DUNELM.), PH.D. (EDIN.), University of Edinburgh, and D. M. DUNLOP, B.A. (OXON.), M.D., F.R.C.P. (EDIN.), F.R.C.P. (LOND.), Christison Professor of Therapeutics and Clinical Medicine, University of Edinburgh. 5th ed. Pp. 342; 30 ills. Edinburgh and London: E. & S. Livingstone Ltd., 1958 (The Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $6.75.

THIS is the fifth edition of a well-known guide to the practical use of chemistry in clinical medicine. As before, emphasis is placed on a knowledge of the circumstances in which a chemical examination may be helpful to the clinician, on the interpretation and signficance of results, and on the technique of obtaining specimens for laboratory tests.

The present edition is up-to-date and should continue to be as valuable to clinicians as its predecessors. C.Z.

PRATIQUE DU LABORATOIRE. By C. JAULMES, A. JUDE, AND J. Q. DES ESSARTS. 2nd ed. Pp. 872; 50 ills. and 5 plates, 1 in color. Paris: Masson et Cie, 1958. Price, 7.600 fr.

THIS is the second edition of a comprehensive practical laboratory manual in the French language. The presentation is conventional, with major sections devoted to general laboratory techniques, biologic tests, biochemical procedures, hematology and serology including immunohematology, parasitology and entomology, and pathologic anatomy.

The volume is well illustrated with numerous tables and charts. The only plate in color depicts the cellular blood elements in perhaps too schematic fashion. Otherwise, the text should be adequate for standard practical reference purposes. C.Z.

DISEASES OF THE NERVOUS SYSTEM. By SIR FRANCIS WALSHE, M.D., D.Sc., F.R.S., Consulting Physician to University College Hospital and to the National Hospital for Nervous Diseases, Queen Square, London. 9th ed. Pp. 373; 60 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $8.00.

IT is with mixed emotions that this reviewer sits down to write of this book by an outstanding English neurologist. In the preface to the first edition the author speaks of "writing a simple textbook adapted to the needs of the student and the practitioner" and "giving this circle of readers all they need and no more." This has been admirably accomplished but in the process it is the feeling of this reviewer that not enough is included.

Treatment in particular is too briefly considered. It is, therefore, incomplete by the standards in this country. Drugs are recommended which have passed out of use here and others are suggested in doses below those accepted here. In some conditions seemingly well established preparations are not mentioned. The brevity of the book could be partially, at least, counterbalanced by an adequate list of references to which the reader could refer. Such is lacking.

On the other side of the ledger the author's true colors as a clinical neurologist shine

through in his considerations of physical therapy as palliative, not curative, of nervous diseases, together with his refusal to be stampeded into that which is still unproved. The fact that the book is not encyclopedic leads to another good point in its favor, its price. Then, too it is one neurological textbook which properly covers the subject of the neurologic involvement associated with pernicious anemia, especially concerning treatment. This is not always the case with American texts. The treatment of Parkinsonism is excellent.

New material has been added especially a chapter on the neurological complications of liver disease and a brief account of hepatolenticular degeneration. There is, as before, a brief consideration of the neuroses and the neurological examination which the writer believes belong in any book of this type.

The book is recommended with reservations. S.G.

CONNECTIVE TISSUE: A SYMPOSIUM. Edited under the direction of R. E. TUNBRIDGE, University of Leeds, by MADELINE KEECH, J. F. DELAFRESNAYE, AND G. C. WOOD. Pp. 371; illustrated. Springfield, Ill.: Charles C Thomas, 1958. Price, $8.50.

THIS volume contains the proceedings of a symposium on connective tissue which was organized by the Council for International Organizations of Medical Sciences (jointly sponsored by UNESCO and WHO) and held in London in 1956.

A number of basic discussions regarding collagen and related substances are included. For example, the following are among the topics considered: the structure, functions and topographical cytochemistry of tissue mast cells; the fibrinogenesis of collagen; the acid mucopolysaccharides of connective tissue; reactions to injury of vascular elastic membranes and associated polysaccharides; reticulin; elastin; the structure of a chondroitin sulfate complex from cartilage; and the amino-acid sequences of collagen.

These and the remaining papers are fundamental treatises on various aspects of this important tissue. Investigators concerned with the biochemistry of collagen disorders will find this a most valuable and stimulating volume. C.Z.

SOME MILESTONES IN THE HISTORY OF HEMATOLOGY. BY CAMILLE DREYFUS, M.D. Pp. 87; 16 ills. New York and London: Grune & Stratton, Inc., 1957. Price, $4.50.

THIS is a readable and enjoyable account of certain selected landmarks and milestones in the progress of Hematology. Included are the following chapters: A Glance at the History of the Blood; Chronic Hemolytic Jaundice; Notes on the Early History of Leukemia; A Historical Survey of the Clinical Picture of Plethora Vera; and Georges Hayem.

Hematologists and other internists as well as all students of medical history will find much pleasurable and interesting reading in this small volume. C.Z.

POLIOMYELITIS: PAPERS AND DISCUSSIONS PRESENTED AT THE FOURTH INTERNATIONAL POLIOMYELITIS CONFERENCE. Compiled and edited for the International Poliomyelitis Congress. Pp. 684; 422 ills. Philadelphia: J. B. Lippincott Co., 1958. Price, $7.50.

THIS is a most interesting compilation of the status of knowledge concerning poliomyelitis and allied viral diseases in 1957, as described and discussed at an international congress participated in by authorities from all over the world. I.W.

A DOCTOR REMEMBERS. BY EDWARD H. RICHARDSON, M.D., Associate Professor Emeritus of Gynecology, Johns Hopkins University School of Medicine. Pp. 252; 4 ills. New York City, Washington, Hollywood: Vantage Press, Inc., 1959. Price, $3.95.

As one progresses through this informal autobiography, the promise of the opening paragraph of the Foreword is found well confirmed. The frequent anecdotes that fill most of the 11 chapters make easy reading, and incidentally help in rounding out the picture of the narrator himself. His modest denial of any claim to literary excellence of epoch-making achievement further lubricates perusal, though the result might be more fitted for a privately printed text for distribution to friends and relatives. The general reader, far from being shocked by the selections, may be more apt to complain of their trivial dullness. But we have no quarrel with any egotistic qualities displayed. After all, without them there would be no autobiographies, and the world's literature would have lost much.

When Dr. Richardson reaches the colleagues at the Johns Hopkins Hospital with whom he had personal contact, the narrative becomes more fertile. Readers of Hopkins

memoirs should no longer be irritated by such unqualified sentences as "the most competent and stimulating group of medical educators in America"—though if the sentence were preceded by "one of" it would more surely be accurate and also add a bit to the modest denial quoted above.

We hope that readers of this naive production will get as much pleasure from it, or almost as much, as the author got in writing it. E.K.

THE BIOCHEMISTRY OF CLINICAL MEDICINE. By WILLIAM S. HOFFMAN, PH.D., M.D., Professorial Lecturer in Medicine, University of Illinois College of Medicine. 2nd ed. Pp. 734; 62 ills. Chicago: The Year Book Publishers, Inc., 1959. Price, $12.00.

THE present edition of this textbook of clinical biochemistry has maintained the high excellence of its predecessor. Again, the author has made a readable and interesting presentation of the fundamental biochemical aspects of clinical medicine. As is to be expected, the revised text includes many new topics, for example, serum mucoproteins, malignant carcinoid syndrome, Wilson's disease, agammaglobulinemia, galactosemia, cryoglobulinemia, oral hypoglycemic agents, oral diuretics, serum transaminase, and hypofibrinogenemia. In addition, a large number of sections have been entirely rewritten in order to incorporate newer information and concepts.

This book is recommended to all physicians. It requires no more than the usual amount of training in chemistry and physiologic sciences in order to understand and apply the encompassed information in clinical medicine. C.Z.

THE STRUCTURE AND FUNCTION OF SUBCELLULAR COMPONENTS. Biochemical Society Symposium Number 16. Edited by E. M. CROOK. Pp. 100; illustrated. New York: Cambridge University Press, 1959. Price, $4.25.

THIS series of papers presented at a Biochemical Society Symposium in London in 1957, seeks to explore the problems of the distribution of cellular components on the basis of whether or not real localization exists. Is there a more than incidental and temporary interaction and relationship between subcellular components?

The papers include a review (124 references) of material on the ultra-structure of cell membranes and cell organelles; cytochemical staining in regard to intra-cellular enzyme distribution and experiments relating this to total cell function; the relationship of structure to function for simple cells and changes in liver injury are also discussed.

This is an extremely stimulating and thoughtful series of papers opening up a new dimension in our thoughts and in the investigation of cell function. It should prove a fruitful avenue for further study. J.B.

CELL AND TISSUE CULTURE. By JOHN PAUL, M.B., CH.B., PH.D., M.R.C.P. ED., University of Glasgow. Pp. 261; 41 ills. Edinburgh: E. & S. Livingstone, Ltd., 1959 (The Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $7.00.

DR. PAUL has produced a textbook of cell and tissue culture that should be purchased by many biologists.

Although it is principally a book of methodology, it is by no means a "cookbook." One whole section, for example, is devoted to cell structure, metabolism, and environmental needs, including the kinds of media which supply them. Quite properly, standard procedures receive the most attention, but special techniques such as "organ" culture and trypsinization are also discussed. The final section is devoted to the use of autoradiography, electron microscopy, cinemicrography, and others, to the applications of cell and tissue culture in metabolic studies, and to virologic research.

Here is a small, lucid, and adequate text for beginners and intermediates. It developed from the annual Tissue Culture Association Summer Course given at Denver, Colorado, of which Dr. Paul is director. He is to be congratulated for rendering a service to others who cannot attend that course. And finally, mention must be made of the appropriate illustrative drawings, complete index, and well chosen chapter references. E.S.

HORMONES AND ATHEROSCLEROSIS. Edited by GREGORY PINCUS. Pp. 484; illustrated. New York: Academic Press, Inc., 1959. Price, $13.50.

A CONFERENCE on the role of hormones in atherosclerosis was held in Brighton, Utah, in March, 1958. The papers and the discussions provoked by them have been recorded in this volume. The subject matter is extensive, including the biosynthesis of cholesterol; the formation and metabolism of bile acids; the conversion of C^{14}-acetate to cholesterol; the

arterial wall as an organ; experimental stress as related to blood lipids; the effect of adrenals, pituitary, liver, and mucopolysaccharides on blood lipids; possible relationship of the emotions to clinical coronary heart disease; the effects of sex hormones on serum lipids and lipoproteins; and many other important aspects of this general field.

Clinical investigators and those working in relevant basic sciences will find this an invaluable reference volume. C.Z.

TRAITÉ DE BIOCHIMIE GÉNÉRALE. Edited by P. BOULANGER, University of Lille, France, and J. POLONOVSKI, University of Paris, France. Pp. 1476 (two volumes); 190 ills. Paris: Masson et Cie, 1959. Price, 22,000 fr. ($45.00).

THIS work is the first portion of an extremely valuable and complete treatise on general biochemistry. This first section, published in two volumes, seeks to outline the chemical composition of living organisms. The exposition is basically chemical; first elementary composition; then water and the principle mineral substances found in living material are discussed. The organic constitution is divided into headings under carbohydrates, lipids, and proteids (amino acids up to proteins). Volume II of the first section deals with proteins, and protein complexes (glycoproteins, phosphoproteins, nucleoproteins and chromoproteins). A section is included on amines, alkaloids and lipoprotein complexes. This is an extremely detailed effort, including, for example analytical data for many substances in various species, in various organs and variations with geographical location. Interpretation of the role of these substances and of the importance of their interactions are a major contribution to the work.

The succeeding sections to be published in 1960 and 1961 will cover the biocatalytic reactions and include vitamins, enzymes, transmitters and hormones (Vol. II). Section III will delineate biochemical synthesis and degradation and their coordination.

This is a well planned, beautifully executed work showing a great amount of biochemical insight. J.B.

The Physical Foundation of Biology. BY WALTER M. ELSASSER, Professor of Theoretical Physics, University of California, La Jolla. Pp. 219; 16 ills. New York: Pergamon Press, Inc., 1958. Price, $4.75.

DR. ELSASSER is a well known theoretic physicist. The over-all purpose of this book is to consider the difference between an organism and an automaton. This he does in an impressive manner. Cybernetics and "information theory" are considered in the first part of the book. Thus is provided an approach to many philosophical problems. The book is not mathematical or technical in its emphasis. Chapters are included on Feedback and Control, Information, Storage and Memory, Structure and Variability, and Microscopic Measurement. M.O.

Elements of Biophysics. BY JAMES E. RANDALL, B.S.E.E., M.S., PH.D., Associate Professor of Physiology and Biophysics, University of Missouri Medical Center. Pp. 322; 74 ills. Chicago: The Year Book Publishers, Inc., 1958. Price, $8.00.

THIS book is an important contribution intended for the level of first year medical students and for graduate students in biology. It presents the basic concepts of biophysics which can be applied to biology and medicine. It serves as a link between physical concepts at the college level and those applied in biological and medical areas.

The illustrations are lucid and well chosen. All sections are well presented. The short section on statistics is especially rewarding where a student meets biometry for the first time.

M.O.

The Teaching and Learning of Psychotherapy. BY RUDOLF EKSTEIN, PH.D. AND ROBERT S. WALLERSTEIN, M.D. The Menninger Foundation. Pp. 334. New York: Basic Books, Inc., 1958. Price, $6.50.

THIS book contains perceptive observations about administration, supervision, the retreats from and aggressive advances upon authority, and the clear delineation that the way a student, therapist, teacher, or administrator handles a situation is characteristic and useful in the process of understanding teaching. It could be shorter and less unevenly written. The authors appear to accept the idea that psychotherapy is the basis for the formation of a separate extramedical profession. They imply that training in psychiatry puts very little emphasis upon psychotherapy: "Psychiatric residency programs require basic training in diagnostic work, in ward and hospital management, in somatic therapies, in neurology, in working with the related professions, and also in psychotherapy." It appears that their residents have limited amounts of training and supervision in psychotherapy, while at the reviewer's institution, it continues 2½ years of the three.

The book is well worth reading, and for administrators and supervisors, Chapters II, III, XI, and XV could be considered required.

F.H.

Photoreception. BY JEROME J. WOLKEN, AND 32 OTHERS. Pp. 245; illustrated. New York: New York Academy of Sciences, 1958. Price, $3.50.

AN excellent presentation of the structure, biochemistry, and physiology of photoreceptors and

photoreception is contained in this report of a conference on these subjects. The participants are all members of high standing and the reports are in great detail. The electrophysiology of the eye is particularly well presented. M.O.

Psychosomatic Correlation in Its Biochemical Aspect. By P. Puig Muset. Pp. 59; 8 ills. Barcelona, Spain: P. Puig Muset, 1958.

There is a molecular substratum to the central nervous system in addition to the histologic and anatomic substrata. "In the final phase of many reactions effecting the central nervous system, some bodies of extremely simple molecular structure are formed; namely ammonia (NH_3) and hydrogen peroxide (H_2O_2). Also, the simpler derivative radicals: oxidrile (OH) and hydroperoxo (O_2H); there are electronically incomplete structures unable to exist in isolation." These compounds may have a fundamental importance to an understanding of the vegetative functions and psychic activity of the central nervous system.

The manuscript, apparently translated from the Spanish, is a very poor translation. The English grammar and spelling at points are difficult to understand. M.B.

Essentials of Therapeutic Nutrition. By Solomon Garb, M.D., Associate Professor of Pharmacology, Albany Medical College. Pp. 147. New York: Springer Publishing Co., Inc., 1958. Price, $2.00.

This a brief and informative book on nutrition directed primarily to nurses for improving their understanding of nutritional regimens and diet therapy. It is written in an interesting style, with emphasis placed upon salient points in the relationship between diet and recovery from disease and maintenance of health. Therapeutic diets occupy a section of the book in which is described virtually all diets employed in patient management. This book should be compulsory reading for all graduate nurses and has much to offer as collateral reading for medical students and physicians. C.S.

Young Children in Hospitals. By James Robertson. Pp. 136. New York: Basic Books, Inc., 1958. Price, $3.00.

Some psychologic damage often results from a hospitalization experience, especially with youngsters under 5 years of age. Written by a child psychiatrist working in the Tavistock Child Development Research Unit in England, this little book describes those pertinent practices and attitudes in hospitals which fail to take into account the emotional needs of sick children and their parents, and makes specific recommendations for their correction. I.W.

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Dr. Richard A. Kern, Temple University Hospital, Philadelphia 40, Pa.

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